SURGERY
Gynecology & Obstetrics
SEPTEMBER 1961
VOLUME 113
NUMBER 3

ACUTE OBSTRUCTIVE SUPPURATIVE CHOLANGITIS

FRANK GLENN, M.D., F.A.C.S., and FRANK G. MOODY, M.D., New York, New York

OBSTRUCTION AND INFECTION are common manifestations of biliary tract disease. They may be present alone or in combination and display a wide variety of signs and symptoms which depend upon the degree of obstruction and the virulence of the infecting organisms. When complete obstruction to bile flow occurs within the common duct or one or more of the major intrahepatic ducts in the presence of pathogenic enteric bacteria, an overwhelming, catastrophic syndrome often develops. It is characterized by the sudden onset of severe right upper quadrant abdominal pain which is unremitting. Chills, fever, and progressive obstructive jaundice follow. The liver enlarges and becomes exquisitely tender. An extremely septic course ensues. The patient becomes markedly toxic and lapses into a progressive coma which is followed by vasomotor collapse and death.

This dramatic syndrome has been descriptively termed acute obstructive suppurative cholangitis. It is indeed a suppurative process in which frank pus is present under pressure within the dilated extrahepatic and intrahepatic biliary tree. Seeding of the blood stream probably occurs in most patients, but the demonstration of bacteremia by blood culture is not always accomplished. The obstruction is most often on the basis of stone within the common bile duct or biliary radicles, but may be secondary to stricture or carcinoma of the bile duct, and rarely is due to a lesion arising in the pancreas or duodenum.

In 1889, Rogers accumulated 20 postmortem cases of suppurative cholangitis. He accurately described the clinical features of this disease and recognized the role of surgical therapy. With the knowledge gained from this experience, he was able correctly to diagnose a case antemortem in 1902. He instituted free drainage of the biliary tree by a glass tube inserted into the common duct. The patient died on the morning after the operation. Grant reported 3 cases in 1945. Cole reviewed the clinical aspects of this disease in 1947 and reported 4 cases. Reynolds and Dargan emphasized the importance of surgical therapy with 5 illustrative cases in 1959. Hampson, Dickison, and Robertson affirmed the urgent nature of operative decompression of the biliary tree in 2 cases reported in 1960. The following 8 cases encountered on the pavilion services of The New York Hospital-Cornell Medical Center since 1932 demonstrate the many problems associated with the diagnosis and treatment of this disease.

From the Department of Surgery, The New York Hospital-Cornell Medical Center, New York.

REPORTS OF PATIENTS

PATIENT 1. A 55 year old housewife was admitted to The New York Hospital for the third time on 12 August 1960 with a 3 hour history of severe, crampy, right upper quadrant pain without chills, fever, or jaundice. A cholecystectomy and choledocholithotomy had been performed in November 1958 for long-existing calcareous biliary tract disease. Stones were again removed from the common duct as well as the intrahepatic biliary tree in April 1959. Residual stones were demonstrated, and accordingly she was maintained on T-tube drainage until December 1959. The T tube was removed at that time and she continued symptom-free until the sudden onset of her present illness.

Examination revealed an acutely ill, swarthy female without apparent clinical icterus. Her blood pressure was 150/70 millimeters of mercury, the pulse was 80, and the temperature was 38.1 degrees C. There was tenderness to deep palpation in the right upper quadrant of the abdomen; the liver was not palpable. The white blood cell count was 13,800 with a marked shift to the left, total bilirubin was 11.8 milligrams per cent, alkaline phosphatase was 7.6 Bodansky units, and serum transaminase was 338 units.

She was initially observed in the emergency room for a 12 hour period at bed rest. Hydration was carried out with parenteral fluids. Procaine penicillin, 1.2 million units, and streptomycin, 0.5 grams, were given every 6 hours. The right upper abdominal pain became more severe, and temperature rose to 38.5 degrees C. Pseudomonas pyocyaneus was cultured from the blood stream. Four grams of chloramphenicol were administered intravenously. Twenty-four hours after admission the blood pressure dropped to 75/50 millimeters of mercury; the pulse, which was 80 on admission, rose to 144. Norepinephrine was administered by intravenous drip to maintain an adequate blood pressure. In spite of the patient's extremely critical condition, common duct decompression was embarked upon.

An enlarged and tense common duct measuring 1.5 centimeters in diameter was readily apparent. A moderate amount of cloudy bile admixed with calcareous debris issued forth as the common duct was incised. After the removal of a large calculus proximal to the choledochotomy, frank pus gushed forth under pressure. Approximately 25 small stones were removed and a T tube was secured in the duct. Norepinephrine was administered throughout the operation and in decreasing amounts for the ensuing 12 hours. Administration of penicillin, streptomycin, and chloramphenicol was continued for 48 hours and was then replaced by oral tetracycline, 500 milligrams every 6 hours. Daily T-tube irrigations of saline by gravity resulted in progressive clearing of the heavily sedimented bile. She was discharged on the twenty-third postoperative day. Gravity irrigations were continued daily by a visiting nurse. Readmission was required 2 weeks after discharge for an episode of cholangitis which responded to reinstitution of tetracycline therapy. The T tube was removed at that time. She has since remained free of biliary tract symptoms, a period of 8 months.

Obstructive suppurative cholangitis was suspected early in the course of this patient's illness in view of the long-standing history of biliary tract disease. In spite of this, the course was rapidly progressive and far advanced before operative decompression was performed. The patient's poor response to broad antibiotic coverage is characteristic of this disease. Supportive measures to include blood transfusion and norepinephrine were essential when shock ensued. The importance of operative decompression, which was undertaken in spite of the patient's extremely critical condition, is well illustrated. The dramatic response to free drainage is characteristic of the result obtained when closed infections in any area of the body are released. The striking feature of such an infection in the biliary tree is its rapid and devastating course until operative decompression is performed.

PATIENT 2. A housewife, 47 years of age, was admitted on 7 March 1960 with a 1 week history of recurrent episodes of chills, fever, light stools, and dark urine. This group of symptoms had been preceded by several days of anorexia and nausea. Vague upper abdominal discomfort was present, but no frank pain. She had been in excellent health throughout her life up to that time.

Examination revealed an acutely ill, deeply jaundiced female. There was no abdominal tenderness. The liver was percussed 3 centimeters below the right costal margin but could not be palpated. The hemoglobin was 9.8 grams, the hematocrit 29.5 per cent, the white blood cell count was 25,100 with 93 per cent neutrophils, total bilirubin was 24.8 milligrams per cent, alkaline phosphatase 25.4 units, cephalin flocculation 2.0 units, and serum transaminase 62 units. Blood cultures were negative.

The presumptive diagnosis on admission was infectious hepatitis, and accordingly a high caloric diet was encouraged. The patient's condition deteriorated rapidly over the ensuing 24 hours, the temperature rising to 40 degrees C. Parenteral fluid replacement was instituted, and the administration of 250 milligrams of tetracycline every 6 hours was started without beneficial effect.

Exploration of the abdomen on the third hospital day revealed a hugely distended, jaundiced liver. The gallbladder was thick-walled and contracted and contained stones. Aspiration of a markedly enlarged common duct produced bile mixed with pus. Incision of the duct allowed 300 milliliters of bile and purulent material to escape under pressure. A solitary stone completely occluding the common duct was removed from the region of the ampulla. Several stones were removed from the gallbladder, and a tube cholecystostomy was performed. A T tube was secured in the common duct. Culture of the bile revealed Escherichia coli. Cholecystectomy was deferred in order to decrease trauma to the extensively inflamed liver.

Two grams of tetracycline per day and 1 gram of chloramphenicol each day were administered intravenously for 7 days. The patient's temperature promptly dropped to normal on the day after operation, and the remainder of the postoperative course was uneventful. Both tubes were removed at 2 weeks after a patent and normal biliary tree had been demonstrated by cholangiogram. An interval cholecystectomy was performed on 14 June 1960, 3 months after biliary decompression. The common duct was moderately thickened but otherwise normal at that time. She has remained well to date, now 9 months later.

The preoperative diagnosis of suppurative cholangitis is difficult when a history of biliary tract disease is not present. When this illness is the primary manifestation of biliary tract disease, as in the case just cited, delay in correct diagnosis is common. Once the diagnosis is suspected, operative decompression of the biliary tree is mandatory. Delay may result in death of the patient. Decompression should be performed in the most direct and simplest manner. Definitive operation is deferred until such time as the patient fully recovers from this illness. To impose a prolonged and complicated procedure would in a high percentage of cases negate the success which can be accomplished by surgical decompression of the obstructed ductal system. This patient's pathologic process and decompression procedure are illustrated in Figures 1 and 2.

PATIENT 3. A 65 year old Puerto Rican male was admitted in July 1958 with a 4 day history of intermittent crampy right upper quadrant abdominal pain and progressive jaundice without chills or fever. He had been treated in the outpatient department for a chronic peptic ulcer for 2 years. An oral cholecystogram 1 year prior to admission was normal.

Examination revealed an icteric, moderately ill male complaining of severe right upper quadrant pain. His temperature was 37.9 degrees C., the pulse was 92, and the blood pressure 160/100 millimeters of mercury. There was marked tenderness in the right upper quadrant of the abdomen with a sensation of fullness beneath the costal margin, but a palpable liver edge could not be felt. The hematocrit was 45 per cent, the white blood cell count 30,200, the total bilirubin 12.6 milligrams per cent, alkaline phosphatase 18.0 Bodansky units, and amylase 275 Somogyi units.

Decompression of the biliary tree was performed on the day after admission. The gallbladder was distended and thick-walled and contained many small brown stones. The pancreas was thickened and boggy with numerous areas of fat necrosis on the surface of the gland. The common duct measured 2.5 centimeters in diameter and was markedly distended. Decompression of the gallbladder did not relieve this distention. Incision into the common duct released thick, purulent bile which revealed Aerobacter aerogenes on culture. A stone was impacted in the ampulla of Vater. This was removed as well as several stones within the proximal biliary tree. A T tube was secured in the common duct after cholecystectomy had been performed. An uneventful recovery followed. A normal cholangiogram was obtained 3 weeks after operation and the T tube was removed. He was last examined 2 years later in July 1960. He had remained free of symptoms referable to biliary tract disease.

A striking feature of this case is the absence of chills or fever. The extensive nature of the inflammatory disease, however, is reflected in the marked leukocytosis, and it was this finding along with the patient's over-all clinical picture that led to exploration and early decompression of the biliary tree. Of particular interest was the degree of the associated pancreatitis. Pancreatitis in varying degree accompanied each of the cases studied but, in most instances, was mild and limited to induration of the head of this organ and not a generalized or necrotizing process as was found in this patient. Failure to decompress the biliary tree by cholecystostomy emphasizes the importance of incision and exploration of the common duct to insure that adequate drainage is established. Procedures which

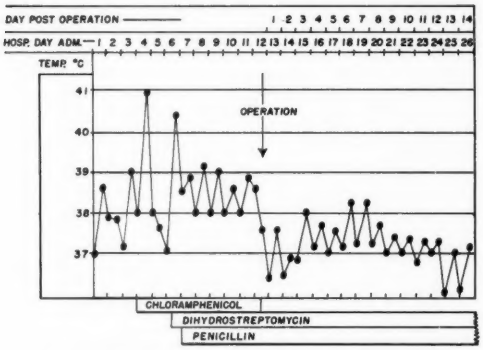


FIG. 3. Daily temperature, Patient 4. Acute suppurative cholangitis in association with common duct obstruction secondary to stone. The septic course was not interrupted by chemotherapy. Dramatic response to T-tube decompression of common duct and choledocholithotomy on twelfth hospital day is shown.

do not establish the free flow of bile from all areas of the biliary tree will not be successful.

PATIENT 4. A 70 year old female entered The New York Hospital in January 1952 with a 3 week history of chills, fever, and malaise. Her illness had not responded to large doses of penicillin. She had had a cholecystectomy in 1948 for empyema of the gallbladder.

Examination on admission revealed an acutely ill, nonicteric woman with a temperature of 37 degrees C., a pulse of 80, and blood pressure of 150/70 millimeters of mercury. There was marked tenderness in the right upper quadrant of the abdomen, but the liver could not be felt. The white blood count was 23,000, the total bilirubin 1.8 milligrams per cent, and alkaline phosphatase 11.2 units.

The patient's temperature slowly rose to 39 degrees C. during the first 3 hospital days. It then spiked to 41 degrees and was accompanied by a shaking chill, severe malaise, and stupor. The bilirubin rose to 6.0 milligrams per cent. A blood culture taken at that time subsequently revealed an Escherichia coli bacteremia. The administration of 500 milligrams of chloramphenicol every 4 hours, with 400,000 units of penicillin twice daily was started. To this was added dihydrostreptomycin, 500 milligrams every 4 hours, without effect on the patient's febrile and extremely toxic course. Decompression of the common duct was carried out on the twelfth hospital day. A large stone was found impacted in the ampulla of Vater. The character of the bile was not described: however, the duct was noted to be remarkably enlarged. Culture of the bile revealed Escherichia coli, Aerobacter aerogenes, and hemolytic streptococcus. The temperature returned to normal and an uneventful course ensued. The T tube was removed on the fourteenth postoperative day and the subsequent course has been symptom-free, now 8 years after operation.

This patient entered the hospital with a smoldering cholangitis without the signs of an obstructive element. Thereafter, a septic state, refractory to intensive antibiotic therapy, rapidly developed and led to abdominal exploration. The dramatic effect of decompression of the biliary tree is well demonstrated in the temperature chart (Fig. 3). The persistence or return of low grade fever in the early postoperative period is not unusual and indicates the importance of continuing the antibiotic coverage even when adequate drainage has been established. Release of frank pus from the biliary tree usually interrupts the fatal course of this disease, but it is only by prolonged drainage and effective chemotherapy that the infection within the major bile ducts and biliary radicles can be eradicated.

PATIENT 5. A 75 year old male entered The New York Hospital for the seventh time on 5 July 1960 with a 5 day history of diurnal chills and fever, anorexia, progressive jaundice, and right upper quadrant abdominal tenderness without overt abdominal pain. He had had a cholecystectomy in 1955 for chronic cholecystitis. In July 1958 and April 1959 stones were removed from the common duct. He then remained without symptoms until the onset of the present illness.

Examination revealed an acutely ill male with slight scleral icterus. The temperature was 40.6 degrees C., the blood pressure was 140/70 millimeters of mercury, and the pulse was 88. There was moderate right upper quadrant tenderness; the liver could not be palpated. The white blood cell count was 16,700, total bilirubin 1.9 milligrams per cent, and alkaline phosphatase 5.4 Bodansky units. Blood culture made on admission later revealed a Pseudomonas pyocyaneus bacteremia.

Tetracycline was administered intravenously for 24 hours and was then continued intramuscularly, 2 grams a day, in divided doses. Sensitivity studies revealed the bloodborne organisms to be resistant to all antibiotics except polymixin B. Kanamycin and chloramphenicol were given for 36 hours and then discontinued because of a rash. Tetracycline was continued, and on this therapy the patient's temperature returned to normal and the general condition improved.

Exploration revealed the common duct to be thick-walled and dilated to 1.5 centimeters. Choledochotomy released a small amount of stone-flecked bile. Removal of stones in the proximal duct, however, released a thick yellow-brown purulent material which cultured Pseudomonas pyocyaneus and enterococci. The postoperative course was uneventful. A delayed cholangiogram, however, revealed a residual stone in the left hepatic duct. The patient has been managed in the outpatient department with a T tube in place on daily irrigations by gravity with sterile saline. He has remained free of symptoms for 10 months. Reoperation for the removal of the calculus has been recommended.

Obstructive suppurative cholangitis was not recognized in this instance prior to operation. A diagnosis of ascending cholangitis was suspected upon admission. An associated obstruction was not considered in the presence of only mild jaundice and a normal alkaline phosphatase. Antibiotic therapy was effective, even though the bloodborne organism was not sensitive to those prescribed. The response to antibiotic therapy is demonstrated in Figure 4.

Exploration of the biliary tree revealed the obstruction to be confined to the proximal bile ducts, possibly to only the left hepatic duct. In spite of several attempts to clear this ductal system of calculi, a persistent shadow remained on delayed cholangiography. The patient is being maintained on biliary drainage as a safety measure until another attempt is made to remove the calculus.

PATIENT 6. A 64 year old housewife was admitted on 22 December 1945 with a 2 week history of upper abdominal pain, nausea, vomiting, light stools, dark urine, and progressive lethargy. She had had a cholecystectomy 25 years prior to this admission.

Examination revealed a moderately icteric, extremely lethargic white female. The abdomen was protuberant. The liver was palpated 2 fingerbreadths below the right costal margin and was markedly tender. The temperature on admission was 37.6 degrees C., the white blood cell count was 21,400, and the icteric index was 35.

The patient's general condition improved remarkably with hydration and transfusion. The temperature, however, rose to 40 degrees C. over the ensuing 9 days. The white blood cell count rose to 37,600 and the icteric index to 45. A progressive stupor ensued. The blood pressure dropped to 40/20 millimeters of mercury and remained below 90 systolic for 5 days. Twenty-five thousand units of penicillin were administered every 3 hours during this period. A diagnosis of suppurative cholangitis was suspected but operation was deferred because of her extremely poor condition. She continued with a markedly septic course and died on the thirty-sixth hospital day.

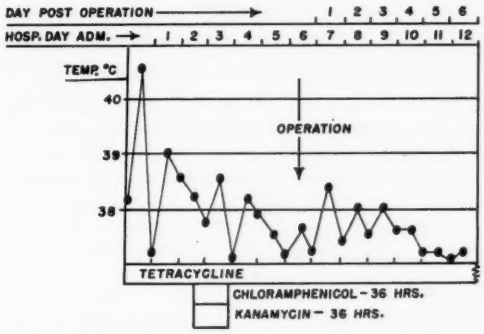


FIG. 4. Daily temperature, Patient 5. Cholangitis responded to antibiotic therapy. Frank pus was released from within the left hepatic ductal system on the sixth hospital day. Numerous stones were removed from the common bile duct and proximal biliary tree. T-tube decompression of common duct was instituted.

Postmortem examination revealed the lumen of the common duct to be completely occluded by a 3 by 1.5 centimeter stone impacted in its midaspect. There was marked dilatation of the proximal biliary tree with multiple abscesses within the substance of the liver. There was an associated pyelophlebitis with purulent material and an organized thrombus within the portal vein. Histologic examination of the common bile duct revealed it to be thickened by fibrous tissue and infiltrated by lymphocytes and neutrophils. The blood vessels within its wall were dilated and filled with bacilli mixed with blood. Cultures of the heart's blood and liver abscesses yielded Escherichia coli.

The course of this patient is typical of the natural history of obstructive suppurative cholangitis when operative decompression is not performed. The patient's biliary tract infection ran an indolent but progressive course. The correct diagnosis was not suspected until the patient was moribund. Decompression prior to this phase might well have been lifesaving. The low dosages of penicillin were administered in accordance with the principles of its use at that time, in 1945, and had no effect upon the overwhelming infection. Extension of the process into the portal vein with a secondary

pyelophlebitis reflects the virulent nature of this infection when complete obstruction to bile flow is present.

PATIENT 7. A 34 year old housewife entered The New York Hospital on 16 March 1938 for the first time with a 2 year history of intermittent obstructive jaundice. One month prior to admission severe crampy right upper quadrant abdominal pain developed accompanied by progressive jaundice, chills, fever, and marked weakness. Past history revealed that a cholecystectomy had been performed in 1934 for jaundice which began 2 weeks after the delivery of the patient's second child. Within a year of this operation a common duct exploration was performed for recurrent jaundice. A normal common duct without stones was reported to have been found. Intermittent jaundice continued until the onset of the present illness.

Examination revealed a well nourished, deeply icteric, acutely ill female whose temperature was 38.2 degrees C., pulse 96, and blood pressure 100/60 millimeters of mercury. The spleen was enlarged and tender. There was tenderness on deep palpation over the right upper quadrant of the abdomen but the liver was not palpable. The white blood cell count was 14,500, and the icteric index 60.

During the first 48 hours she remained febrile but her general condition improved with hydration and blood transfusions. The onset of a moderately severe, constant midepigastric and periumbilical pain suddenly developed which had not previously been present. She remained afebrile for the following 2 days and then began to spike temperatures to above 39 degrees C. The white blood cell count rose to 22,300. She lapsed into coma and died on the twelfth hospital day.

Postmortem examination revealed the biliary tree to be greatly dilated and thick-walled. An area of partial stenosis was present 5 centimeters from the ampulla of Vater. A large stone was lodged just proximal to this area. The duct proximal to this point measured 3.5 centimeters while that distally measured 1.9 centimeters. Just cephalad to the area of stenosis on the posterior aspect of the common duct was a 3 millimeter perforation into the lesser sac where a large abscess was present. The proximal biliary tree was filled with frankly purulent material which cultured Proteus vulgaris.

The presence of long-standing fluctuating jaundice led to a suspicion of stricture or stone with a superimposed cholangitis. The onset of a new type of pain localized to the midabdomen was noted but not properly interpreted. It is of some significance that this pain was associated with a drop in temperature but a marked rise in the pulse rate. The remainder of the course was progressively downhill to profound coma and death as illustrated in Figure 5. Reconstructing the sequence of events from postmortem examination it appears that the common duct became obstructed at the point of stricture by a calculus. The proximal biliary tree became distended with purulent bile, and a perforation into the lesser sac occurred. This relieved the pressure within the biliary tree, leading to a brief respite from the obstructive suppurative process but led to an overwhelming intra-abdominal sepsis.

PATIENT 8. A 20 year old South American male was admitted in June 1953 with a 5 day history of severe aching right upper quadrant abdominal pain accompanied by nausea and vomiting. He had otherwise been in good health up to that time.

Examination revealed an acutely ill, moderately icteric male. The blood pressure was 95/65 millimeters of mercury, the pulse was 136, and the temperature 40.2 degrees C. There was shock tenderness over the right upper quadrant of the abdomen and tenderness to deep palpation in the midepigastrium. The liver edge was felt 1 fingerbreadth below the right costal margin. The white blood cell count was 20,000, total bilirubin 6.3 milligrams per cent, alkaline phosphatase 7.4 units, and serum amylase 175 units.

The presumptive diagnosis on admission was infectious hepatitis. The course was remarkably septic with temperature ranging from 39 to 40 degrees C. The systolic blood pressure remained below 90 throughout the hospital course. Blood culture yielded Escherichia coli. Oxytetracycline, 250 milligrams intravenously every 4 hours, and dihydrostreptomycin, 3 grams per day intramuscularly, were administered. The diagnosis remained obscure. A pyelophlebitis was suspected. The patient's blood pressure dropped steadily in spite of norepinephrine and cortisone and he died on the third hospital day.

Postmortem examination revealed a cystlike dilatation of the common duct with massive dilatation of the intrahepatic biliary tree. The terminal common duct was stenotic, and its wall was white and without apparent bile stain. There were stones within the acutely inflamed gallbladder as well as in the extrahepatic and intrahepatic biliary tree proximal to the stenosis which contained in addition a bile-stained creamy material that cultured Escherichia coli and Aerobacter aerogenes.

This young male had a rapidly progres-

sive, fulminating course which made diagnosis imperative but extremely difficult during life. Postmortem examination revealed a septic dilatation of the entire ductal system and pancreatic ducts. It was believed that this was due to a congenital defect in the walls of both ductal systems. The nature of the obstruction appeared to be on the basis of edema and stricture in the terminal portion of the common duct. It is possible that a small stone may have lodged in this region to initiate the subsequent fulminating illness. Failure to recognize the true nature of this patient's illness deprived him of his only opportunity for survival.

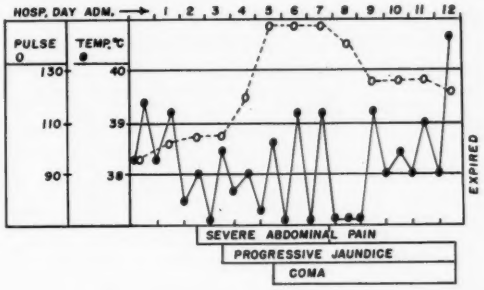


FIG. 5. Daily temperature and pulse, Patient 7. Suppurative cholangitis in association with common bile duct stricture was obstructed by calculus. Spontaneous perforation of common duct occurred on the second hospital day. There was a progressive septic course to death.

DISCUSSION

A successful outcome from this serious disease of the biliary tract demands the utmost in surgical judgment. The diagnosis is not difficult when the typical symptom complex of chills, fever, right upper quadrant abdominal pain, and obstructive jaundice occurs in a patient with long-standing biliary tract disease. When, however, the patient is in the advanced stages of this disease without previous biliary tract symptoms, the diagnosis may indeed be extremely difficult. It should be emphasized that some components of the symptom complex may be lacking. The elderly patient often fails to make a febrile response commensurate with the extent of the disease process. Severe jaundice is sometimes absent, especially when obstruction is limited to only one portion of the biliary tree. Errors in diagnosis are related to an inability to distinguish obstructive from nonobstructive cholangitis when the patient is seen early in his illness, or from far advanced infectious hepatitis when the patient is extremely ill. The diagnosis should be seriously considered when any combination of these symptoms is present and a toxic course progresses in spite of chemotherapy and maximum supportive measures. A high index of suspicion is essential to the recognition of this disease.

Edlund and associates as well as Elkeles and Mirizzi demonstrated that organisms may be cultured from the bile during chronic and acute inflammations of the gallbladder and biliary tree but are most often isolated in association with stones within the bile ducts. The most common organisms encountered are Escherichia coli, Pseudomonas pyocyaneus, streptococcus, Proteus vulgaris and enterococcus. For the most part, they demonstrate a low grade of pathogenicity with only local inflammatory changes within the wall of the bile ducts characterizing their presence. Obstruction to bile flow provides ideal conditions for rapid growth and multiplication of these organisms. When an especially virulent infection is not relieved it may gain access to the liver, extend into the portal vein, and perforate the bile duct, as well as invade the systemic blood stream. Overwhelming septicemia is the usual terminal event.

The exact manner in which enteric organisms gain access to the bile is not known. Three routes are theoretically reasonable: first, the hematogenous, as proposed by Rosenow; second, the lymphatic, as postulated by Graham and associates; and third, the direct ascending infection that traverses the normal sphincter of Oddi. Patey and Whitby studied each of these routes and concluded that the latter is unlikely. However, when normal sphincter function is interrupted by disease, excision,

or bypass of the ampulla of Vater, contamination by enteric laden intestinal contents readily occurs. Operation upon the bile duct with trauma to its mucosa during exploration may well play a role in subsequent inflammatory disease of the biliary tree. Any process which incurs fibrosis of the bile duct wall predisposes to recurrent biliary tract infection. This is especially true of the bile duct stricture. That the diseased bile duct becomes a thickened, rigid tube is an important aspect of the problem. In this state it remains dilated and is unable to empty properly. The common denominator would seem to be bile stasis which enhances further infection and stone formation. A vicious cycle is established which must be interrupted.

The cause of the obstructive element in the disease may be calculi, stricture, congenital anomaly, or carcinoma in or about the bile duct. In our experience reported here, stone could be implicated in each case. One patient had, in addition, a congenitally dilated biliary tree, Patient 8, and a second had a bile duct stricture, Patient 7. We did not encounter a case in which complete obstruction of the bile duct by carcinoma was accompanied by suppurative cholangitis.

The successful treatment of this disease requires operative decompression of the biliary tree. There are several important factors which bear emphasis prior to surgical intervention. Frequent observations of temperature, pulse, blood pressure, and white blood count usually are an index to the trend of the course. General supportive measures to include fluid replacement, blood transfusions, vasopressor drugs, and antibiotics should be employed as indicated. The marked toxicity often present is related to the extremely septic course which accompanies pus under pressure within the biliary tree. Agitation, coma, and vasomotor collapse are manifestations of this course and often are coincident with seeding of the blood stream. Blood cultures are of value in establishing the nature and sensitivity of the predominant organism but from a practical standpoint do not give immediate information. Chemotherapy, however, is usually not effective, even when drug sensitive organisms are known, since antibiotics cannot gain access to obstructed bile. They should be administered, nevertheless, in large doses to combat the blood stream infection and continued in the postoperative period to clear the bile of infecting organisms, as emphasized by Carrigan and McGowan. Chloramphenicol, tetracycline, and streptomycin attain therapeutic levels in the bile after free flow is established, and, as discussed by Larmi and associates, it is these drugs that are most effective against the enteric organisms most commonly encountered.

The primary objective of treatment is decompression by operative drainage of retained pus under pressure within the biliary tree. The surgical procedure should include an attempt to remove the cause of obstruction within the ductal system, but unduly long or complicated maneuvers must be avoided. Cholecystostomy, if the gallbladder is present, is preferred to cholecystectomy. A large T tube may be employed to drain the common duct; the operative area should likewise be adequately drained. Prolonged T-tube drainage is desirable. Frequent irrigations by gravity with sterile saline are recommended, not only to insure patency but also to help clear the heavily sedimented bile which accompanies this disease. Definitive surgery should be deferred until full recovery has occurred. It should then be performed. Procrastination may incur exacerbation of the suppurative process. Definitive surgery is to be directed toward freeing the biliary tree of calculi and re-establishing free flow of bile.

SUMMARY

Eight patients with acute obstructive suppurative cholangitis have been presented. Five survived after operative decompression of the biliary tree. The remaining

3 succumbed to the disease without surgical intervention. Factors which relate to diagnosis, pathogenesis, and treatment are discussed.

REFERENCES

1. CARRIGAN, W. E., and MCGOWAN, J. M. The effect of antibiotic agents on residual biliary infection. Surgery, 1958, 43: 465.
2. COLE, WARREN N. Suppurative cholangitis. Surg. Clin. N. America, 1947, 27: 23.
3. EDLUND, Y. A., MOLLSTEDT, B. O., and OUCHTERLONY, O. Bacteriological investigation of the biliary system and liver in biliary tract disease correlated to clinical data and the microstructure of the gallbladder and the liver. Acta. chir. scand., 1958, 116: 461.
4. ELKELES, G., and MIRIZZI, P. L. A study of the bacteriology of the common bile duct in comparison with the other extrahepatic segments of the biliary tree. Ann. Surg., 1942, 116: 360.
5. GRAHAM, E. A., COLE, W. H., COPHER, G., and MOORE, S. Diseases of the Gall Bladder and Bile Ducts. Philadelphia: Lea & Febiger, 1928.
6. GRANT, H. D. Acute suppurative cholangitis. Permanente Found. M. Bull., 1945, 3: 175.
7. HAMPSON, L. G., DICKISON, J. C., and ROBERTSON, R. H. Emergency surgery involving the biliary tract. Surg. Clin. N. America, 1960, 40: 1171.
8. LARMI, TEURO K. I., FOCK, G., and VUOPIO, P. Occurrence and antibiotical sensitivity of aerobic bacteria in bile and their role in postoperative inflammatory complications in biliary tract diseases. Acta. chir. scand., 1957, 114: 379.
9. PATEY, D. H., and WHITBY, L. E. H. The paths of gall bladder infection; an experimental study. Brit. J. Surg., 1933, 20: 580.
10. REYNOLDS, B. M., and DARGAN, E. L. Acute obstructive cholangitis. Ann. Surg., 1959, 150: 299.
11. ROGERS, LEONARD. Biliary abscesses of the liver with operation. Brit. M. J., 1903, 2: 706.
12. ROSENOW, E. C. Focal infection and elective localization of bacteria in appendicitis, ulcer of the stomach, cholecystitis, and pancreatitis. Surg. Gyn. Obst., 1921, 33: 19.

THE EFFECT OF INTRAVENOUS CALCIUM INFUSIONS UPON THE RENAL RESPONSE FOLLOWING OPERATION

GERALD P. MURPHY, M.D., BENJAMIN F. RUSH, JR., M.D., F.A.C.S., and RONALD H. FISHBEIN, M.D., Baltimore, Maryland

AMONG THE ALTERATIONS in renal function observed after trauma are a retention of water and salt and an increased excretion of potassium and nitrogen. Several factors are known to modify this response. It is roughly correlated with the degree of trauma; it is decreased or lost in the debilitated patient or when one episode of trauma closely follows another; and it is greatly changed by a simultaneous osmotic diuresis, as we have reported (2).

Wolf and Ball, Yoffee and Dingman, and others have shown that intravenous infusions of relatively small amounts of calcium produce an increased excretion of water and of sodium in normal and in edematous individuals. These changes occur in a similar fashion, whether calcium gluconate, calcium lactate, or calcium chloride is given, so that calcium ion seems to be the substance responsible. The changes of renal function produced by calcium ion are not due to an osmotic effect. The exact mechanism is not established but there is some evidence that the effect is mediated in part through a blocking of the antidiuretic hormone of the posterior pituitary. Other investigations suggest that a part of the renal response to intravenous calcium, particularly the increase in sodium excretion, is due to a direct or indirect effect upon adrenocortical hormones. The diuresis produced by calcium infusions occurs despite the injection of small amounts of posterior pituitary hormone and seems enhanced in edematous patients by the administration of adrenocortical steroids. Posterior pituitary and adrenocortical hormones also play a role in the changes in renal excretion observed after trauma. We therefore believed it of interest to observe the effects of intravenous injections of calcium ion upon urinary excretion in patients who were in the early posttraumatic state.

From the Departments of Surgery and Urology of The Johns Hopkins Hospital, the Baltimore City Hospitals, and The Johns Hopkins University School of Medicine, Baltimore.

Supported by Army Grant No. DA-49-193-MD-2016 and N. I. H. Grant No. A2029.

MATERIALS AND METHODS

Thirty patients were selected from the surgical wards for study. All patients were free of renal disease, as judged by a normal blood urea nitrogen and normal urinalysis. Patients were on the regular ward diet and salt was unrestricted. All patients underwent operations on a scale of trauma of 4 to 6, as described by Moore and Ball. The only fluid given postoperatively in the first 24 hours was 1,500 to 2,000 cubic centimeters of 5 per cent dextrose in water. Using methods previously described (2) we made 24 hour determinations of the following: water, sodium, potassium, chloride, and osmolality of the urine. Heights and weights were determined, and all results were readjusted to 1.72 square meters of body surface area.

Of the 30 patients, 10 received no calcium postoperatively; 10 received a single injection of 10 cubic centimeters of a 10 per cent solution of calcium gluconate (0.63 gram of calcium) intravenously within 30 minutes after completion of the operation;

and 10 patients received the same amount of calcium gluconate plus a simultaneous injection of 20 units of vasopressin subcutaneously. This relatively large dose was to insure an overwhelming pharmacologic effect.

RESULTS

The 24 hour volume of urinary excretion in the control patients postoperatively ranged from 490 to 1,770 cubic centimeters, with a mean of 1,169 cubic centimeters. Those patients receiving calcium excreted from 938 to 3,486 cubic centimeters of urine with a mean of 2,296 cubic centimeters, twice the output of the control patients. In patients who received pituitrin in addition to calcium, increase in urinary volume was abolished; volume ranged from 482 to 2,105 cubic centimeters, with a mean of 1,431 cubic centimeters. Excretion of sodium and of chloride, 53 and 63.8 milliequivalents, respectively in controls, also increased in the patients treated with calcium, to 93.4 and 104.4 milliequivalents, respectively, in those receiving calcium, but was 53.4 and 71.6 milliequivalents in those receiving calcium plus the large injection of pituitrin. Urinary potassium was 70 milliequivalents in controls, 38 milliequivalents in patients receiving calcium, and 48.7 milliequivalents in those given both calcium and pituitrin.

The ratio of sodium to potassium excretion was not significantly different in the three groups of patients—.76 in controls, 1.06 in calcium treated patients, and 1.09 in those receiving calcium and pituitrin. Urinary calcium excretion was increased in patients receiving calcium injections. No significant difference was demonstrated in the osmolality of the urine of the three groups of patients.

DISCUSSION

There was no significant difference in the excretion of water, sodium, potassium, or chloride between the untreated patients and the patients receiving calcium plus pituitrin. The significance of the difference between water and electrolyte excretion in the untreated and the calcium treated groups was $<.01$ for water and $>.10$ for both sodium and chloride.

The results demonstrate that intravenous calcium, administered immediately after operation, modifies the normal renal response to trauma. This modification is most notable in the increased amount of water excreted. The difference is quite significant. Sodium and chloride excretion also appear increased, but the difference is less significant. The diminution of water excretion, normally seen postoperatively, is thought to be due to the effect of antidiuretic hormone. If so, this effect was partly or completely blocked by the calcium given. On the other hand, the calcium effect was entirely lost when a very large dose of pituitrin was also administered. This fact suggests that the diuretic effect of a given intravenous dose of calcium is related to the amount of antidiuretic hormone which is present in the circulation.

Patients commonly receive intravenous calcium in the course of operation, especially when multiple transfusions have been given. This fact should be noted if postoperative metabolic or endocrine studies are planned in such patients.

The ratio of sodium to potassium excretion in the urine is thought to reflect adrenal cortical steroid effect on renal function, particularly aldosterone effect. In the normal individual the ratio may be several times unity. Postoperatively it approaches or is below unity. In all of the groups studied the postoperative sodium to potassium ratio approached unity and was unmodified by the administration of intravenous calcium. This observation suggests, but only indirectly, that adrenocortical excretion did not play a role in the renal response to intravenous calcium infusion.

SUMMARY AND CONCLUSIONS

The postoperative administration of a relatively small amount of intravenous cal-

cium modified the expected renal response to trauma. Excretion of water was increased. Excretion of sodium and chloride also increased somewhat. These changes appeared to be due to a blocking of antidiuretic hormone from the posterior pituitary and could be reversed by the administration of a large dose of posterior pituitary hormone. No change relatable to adrenocortical effect on the kidney was demonstrated.

REFERENCES

1. Moore, F. D., and Ball, M. R. The Metabolic Response to Surgery. Springfield, Ill.: Charles C Thomas, 1952.
2. Murphy, Gerald, Fishbein, Ronald, and Rush, Benjamin F. The effect of urea on the postoperative excretion of electrolytes. Surgery, 1960, 48: 485.
3. Wolf, A. V., and Ball S. M. Effect of intravenous calcium salts on renal excretion in the dog. Am. J. Physiol., 1949, 158: 205.
4. Yoffee, H. F., and Dingman, J. F. Studies of effect of calcium on antidiuretic action of vasopressin. Clin. Res. Proc., 1959, 7: 272.

THE ROLES OF CHOLEDOCHOSTOMY AND ANTIBIOTICS IN GALLBLADDER SURGERY

HARRISON J. KORNFIELD, M.D., and FRANK F. ALLBRITTEN, JR., M.D., F.A.C.S.,
Kansas City, Kansas

BECAUSE of interest in the special and exotic fields of surgery it is frequently forgotten that areas of dissatisfaction remain in the more commonplace and day-to-day fields of surgical treatment. Ever since Carl Langenbuch reported the successful removal of a diseased gallbladder in 1882, treatment of biliary tract diseases has become one of the most common undertakings of the surgeon, and one of the most satisfying. In spite of this fact an appreciable number of patients have residual symptoms postoperatively. Although difficult for the surgeon to acknowledge, this figure probably approaches 10 per cent of all patients privileged to undergo operation. This fact, in large measure, accounts for the reluctance of the internist to advise surgical treatment until other methods of management are no longer tolerable.

An incomplete or erroneous diagnosis undoubtedly accounts for a significant number of surgical failures. The necessity for complete and thorough preoperative evaluation is generally acknowledged and will not be considered further. The generally recognized errors of surgical technique which lead to postoperative malcontent are residual cystic duct remnants, injuries to the common duct, and retained common duct stones. Of these, the latter provokes the most concern, for opinion is divided on the proper manner of preventing such an occurrence. There are in general three viewpoints on "silent" common duct stones: (1) elective exploration of every common duct at the time of cholecystectomy; (2) roentgenographic investigation of every common duct at the time of cholecystectomy; and (3) no investigation of the common duct unless indications are present.

From the Department of Surgery, University of Kansas Medical Center, Kansas City, Kansas.

At the University of Kansas Medical Center the procedure of choice varies from service to service. This situation seemed to offer an excellent opportunity for comparing the merits of one approach with the others, since in all other respects the accumulated series is concurrent—the same house staff, parallel thought as to preoperative and postoperative management, and identical ancillary facilities and personnel.

One adjunctive measure was found not to depend upon the type of operation or service but crossed these artificial boundaries; this was the use of antibiotics as prophylaxis following operative intervention. This report concerns, then, the roles of the specific type of operative procedure and the use of antibiotics on the early and late courses after biliary tract surgery.

MATERIAL AND METHOD

All biliary tract surgery performed between 1 July 1953 and 30 June 1958 was reviewed. The records were culled and specific points of interest were transferred to data sheets from which IBM cards were prepared to facilitate statistical investigation. During this period, patients were on one of six services, and the choice of procedure or antibiotic use was dictated by the prejudice of the service. Four hundred and seventy-eight patients were cared for: 88 on service A; 97 on service F; 56 on service H; 26 on service K; 14 on service M; and 197 on the ward. Choledochostomy was

TABLE I.—MORBIDITY

Group	*Wound*	*Genito-urinary infections*	*Pul-monary*	*T-tube compl.*	*Other compl.*	*Total*
I	9	4	5	0	14	32
II	5	1	4	5	5	20
III	5	5	5	12	33	60
IV	0	4	3	0	1	8
Subtotal	19	14	17	17	53	120
V	2	0	1	2	3	8
Totals	21	14	18	19	56	128

TABLE II.—COMPARISON OF POSTOPERATIVE DURATION AND RECOGNIZED MORBIDITY

Group	*Postoperative duration, days*	*Recognized morbidity*	
		No.	*Per cent*
I	8.8	32 of 126	25
II	10.9	20 of 61	33
III	12.2	60 of 192	32
IV	7.6	8 of 45	18
I & IV	8.5	40 of 171	23
II & III	12.0	80 of 253	32
V	10.4	8 of 49	17
VI	16.0	0	

performed in all cases in which the time-proved indications were present; viz., jaundice by history or laboratory demonstration, dilated bile duct, palpation of stone in the common duct, demonstration of stone in the common duct by cystic duct cholangiography, or presence of small stones in the gallbladder. When these indications were not present, the following procedures were available to the surgeon: cholecystectomy per se; cholecystectomy plus choledochostomy, i.e., exploration of common duct with T-tube insertion and drainage, and operative and postoperative cholangiograms; or cholecystectomy plus operative cholangiograms via a catheter inserted through the cystic duct stump. This choice served as the artificial line for dividing the series into groups: group I, 126 cases in which cholecystectomy alone was performed; group II, 61 cases in which cholecystectomy and elective choledochostomy were performed; group III, 192 cases in which cholecystectomy and indicated choledochostomy were carried out; group IV, 45 cases in which cholecystectomy and cystic duct cholangiograms were carried out—3 instances of positive cholangiograms in this group are included in group III; group V, 49 cases of complications of a previous biliary procedure; and group VI, 5 other procedures. Each group was then studied with respect to duration of postoperative stay, in-hospital morbidity, and late complications, and the use of antibiotics was related to these factors. Each group was evaluated in regard to silent choledocholithiasis.

Separately categorized are the patients in group V who were operated on for complications of previous biliary tract surgery, and the group of 5 patients who were excluded from this general categorization for other reasons, such as cholecystostomy.

POSTOPERATIVE HOSPITALIZATION

The interval between operation and discharge is a crude but reliable index of the physiologic insult of an operative procedure. In group I this interval was 8.8 days, in group II 10.9 days, in group III 12.2 days, in group IV 7.6 days, in group V 10.4 days, and in group VI 16 days. Upon combining groups II and III, one finds that operations with a common duct exploration require an average postoperative stay of 12.0 days, whereas cholecystectomy alone (groups I and IV) averages 8.5 days between operation and discharge.

MORBIDITY

A morbid condition was interpreted as any condition that was unexpected or undesirable which occurred in the postoperative period, whether or not it prolonged the postoperative course. Table I lists the incidence and major types of morbidity in this study. The relatively high figures represent third party judgment from perusal of hospital records. Such items as wound infections, pneumonitis, and prolonged T-tube drainage are self-evident; urinary tract infections, fever of undetermined origin, and other types of complications, are often not appreciated while the patient is under clinical study. No attempt is made to separate degrees of morbidity.

The "other" category, group VI, includes mostly temperature of greater than 100.5 degrees per os for more than 2 days as well

TABLE III.—MORBIDITY IN RELATIONSHIP TO USE OR NONUSE OF ANTIBIOTICS AND REASON FOR USE

	No use			*Prophylactic use*			*Indicated use*			*Group total*		
		Morbid			*Morbid*			*Morbid*			*Morbid*	
Group	*No.*	*No.*	*Per cent*	*No.*	*No.*	*Per cent*	*No.*	*No.*	*Per cent*	*No.*	*No.*	*Per cent*
I	30	11	37	63	15	24	33	6	18	126	32	25
II	21	8	38	31	10	32	9	2	22	61	20	33
III	23	9	39	112	34	30	53	17	32	188	60	32
IV	16	6	37	24	2	8.3	4	0	—	44	8	18
	90	34	38	230	61	27	99	25	25			
V	7	2	28	20	4	20	21	2	9.5	78	8	16
Totals	97	36	37	250	65	26	120	27	22			

as such entities as laryngeal edema, hepatitis, moniliasis, drug reaction, prolonged ileus, acute tubular necrosis, and other unforeseen events. Incidence of complications for each group is reported and related to postoperative duration in Table II.

DISCOVERY OF COMMON DUCT STONES

The value of routine choledochostomy lies in the possibility of the discovery of stones or other forms of ductal obstruction which would otherwise be overlooked. None of the indications for choledochotomy were present in the cases comprising group II. Lithiasis was found on 2 occasions, an incidence of 3 per cent. In contrast, stones were found in 68 patients with indications present for choledochotomy, an incidence of 35 per cent.

In 8 instances, sufficient narrowing of the sphincter of Oddi was found during common duct exploration to justify the diagnosis of fibrosis, and dilatation was performed. These cases may represent a "yield" not available with roentgenologic investigation or cholecystectomy alone. Common duct roentgenographic visualization by means of dye injected per the cystic duct was performed in 48 instances (group IV), and defects were seen in 3 patients. In 2 of these, silent stones were found when an exploratory operation was performed, and in 1 there was no lesion. No late biliary sequelae have occurred in these patients, indicating that there were no false negatives.

ANTIBIOTICS

Certain arbitrary criteria for the use of antibiotics were established so that each patient who received these drugs could be categorized into a prophylactic group or indicated group. Antibiotics were assumed to be indicated when: acute cholecystitis was present and diagnosed by both the surgeon and the pathologist; purulent exudate was noted at the time of laparotomy; jaundice was present; an intestinal incision was created during the procedure; or other systemic disease states requiring antibiotic coverage were present. All cases in which these criteria were not fulfilled were included in the prophylactic division.

Antibiotics were subdivided into a broad spectrum type of drug group and a penicillin-streptomycin group but no significant difference was noted between these subgroups.

The data are presented in Table III. No attempt is made to separate degrees of morbidity. As shown by reading vertically, the morbid rate in those patients in whom antibiotics were not used was 37 per cent whereas this rate was but 25 per cent in those patients who received these drugs.

LATE POSTOPERATIVE COMPLICATIONS

Hospital and clinic records were studied for follow-up data. The majority of the patients were seen at least once postoperatively, and clinic patients were seen regularly for total care. All known late postoperative complications are listed in Table IV in relation to antibiotic treatment. Of 90 cases in which no antibiotic was administered, in 10 (11 per cent) late morbidity developed. In 230 instances, antibiotics were given prophylactically and in 17, 7.4 per cent, late complications developed. In 99 patients, antibiotics were used

for indications and in 7, 7 per cent, problems related to their method later developed.

Ten patients had incisional hernias, an incidence of 2 per cent. Nine of the 10 had received antibiotics, 7 for prophylaxis. There were 10 biliary tract complications, an incidence of 2 per cent, and 5 of these occurred in group V patients; that is, in the group that represented previously complicated cases. Thus, 5 *de novo* biliary complications occurred. Two patients in group III had symptoms suggestive of biliary colic on 1 occasion, but in neither instance has exploration been necessary. One patient had had an indicated choledochostomy and stones were found; however, a stone was overlooked and a second operation was required for relief of biliary obstruction. One patient in group II had elective re-exploration for biliary colic with negative findings each time. Another patient had a simple cholecystectomy and recurrent biliary colic developed. Exploration revealed fibrosis of the sphincter of Oddi and sphincterotomy has alleviated her symptoms.

MORTALITY

There were 7 deaths in the entire group, an over-all incidence of 1.5 per cent: 4 in group III, 1 in group IV, 1 in group V, and 1 in group VI. For groups I and IV the incidence was 0.6 per cent, the 1 death occurring in a 58 year old female with arteriosclerotic heart disease who died of cardiac failure on the fifteenth postoperative day. The death rate in the choledochostomy groups (II and III) was 1.6 per cent, but all 4 deaths occurred in the group in which choledochostomy had been indicated. These included death of: a 68 year old female who died of pneumonia on the seventh postoperative day and had received antibiotics prophylactically; a 77 year old male who had a negative common duct exploration and normal operative and postoperative cholangiograms yet had a retained common duct stone causing bile peritonitis after the T tube was removed which resulted in his demise on the 13th day; an 89 year old female who was jaundiced for 6 months prior to operation and died on the sixteenth postoperative day of pneumonia and congestive heart failure; and a 76 year old female who did not receive postoperative antibiotics for prophylaxis and a wound abscess and numerous retroperitoneal abscesses developed with mesenteric artery thrombosis being the direct cause of death. The group VI patient died on the operating table from hemorrhage while dissection was being performed in preparation for a Longmire procedure. The final patient, in group V, had undergone a choledochocholedochostomy in 1951 with recurrence of jaundice in 1954. She then had a choledochoduodenostomy but expired of hepatic failure on the fifteenth postoperative day.

GROUP V

Separately listed from the balance of the data are the figures representing group V. This was done because the purpose of the study demanded that secondary operations on the biliary tract be excluded from the statistics. We included the figures separately, however, because these cases represent part of the "total biliary experience" at the University and because the comparison of these figures with the other groups might be of interest to the reader.

GROUP VI

The 5 patients in this classification underwent operative procedures for biliary tract disease which do not fall into the aforementioned groups. Two patients underwent cholecystostomies, both later followed by definitive operations. One patient had an attempted Longmire procedure and died on the operating table. The other 2 patients had drainage of abscesses without definitive procedures being attempted.

DISCUSSION

The place of elective choledochostomy is unsure. Proponents maintain that it adds

TABLE IV.—LATE POSTOPERATIVE COMPLICATIONS AND RELATIONSHIP TO POSTOPERATIVE USE OF ANTIBIOTICS

Group	*Antibiotics*	*Biliary tract*	*Incisional hernia*	*Minor wound infections*	*Other*	*Subtotal*	*Totals*	*Per cent*
	No use	1	1	1	1	4		
I	Proph. use	0	0	1	0	1		4
	Ind. use	0	0	0	0	0	5	
	No use	1	0	1	0	2		
II	Proph. use	1	1	0	0	2		6.5
	Ind. use	0	0	0	0	0	4	
	No use	1	0	0	2	3		
III	Proph. use	1	5	0	3	9		8
	Ind. use	0	2	0	1	3	15	
	No use	0	0	0	0	0		
IV	Proph. use	0	1	0	1	2		4.5
	Ind. use	0	0	0	0	0	2	
	Subtotals	5	10	3	8		26	
	No use	1	0	0	0	1		
V	Proph. use	1	0	0	2	3		16
	Ind. use	3	0	0	1	4	8	
	Totals	10	10	3	11	10 17 7	34	

little to the operative procedure, is of great value in a preventive sort of way if a stone or other obstructive process is found, prevents unrecognized injury to the common duct by necessitating its dissection, and is unassociated with a significantly increased morbidity or mortality. Opponents say that choledochostomy lengthens the procedure, adds the possibility of operative injury or late stricture to the common duct, is likely to be performed in a perfunctory manner and hence is associated with a small yield of cases of choledocholithiasis as well as with a significantly increased morbidity and mortality.

This retrospective study includes the total experience in biliary tract surgery at the University of Kansas Medical Center over a period of 5 years. Specific indications for choledochostomy were present in 192 or 40 per cent of 478 cases. Stones were present in 35.5 per cent of these cases, a figure lower than the 50 per cent reported by Leichtling but higher than the 16 per cent reported by Colcock. The latter explored the common duct in 45 per cent of his series, a figure comparable to ours.

In the group of patients without a specific indication for exploration 3 per cent were found to have choledocholithiasis. Whether these stones would ever have caused pathophysiologic aberration can never be known, but this finding represents the purpose of exploration. Thus the average duration of hospital stay was extended by 2.5 days and the risk of a recognized complication by 8 per cent. Routine roentgenologic "exploration," on the other hand, as represented by cystic duct cholangiography, was unassociated with prolongation of postoperative recovery or elevation of morbidity. "Positive" operative cystic duct cholangiograms were found in 3 or 6 per cent of 48 cases. One of these was a false positive in that no stones were found at choledochostomy; stones were found in the other 2 patients. Elective choledochostomy appeared to be safe, as no deaths occurred in the 61 patients submitted to this procedure, whereas in the indicated choledochostomy group the mortality rate was 2 per cent. This observation undoubtedly reflects the consequences of the biliary obstruction which caused the patient to be placed in the indicated group. This figure also signifies the importance of alleviating biliary tract obstruction prior to the clinical diagnosis of such involvement—an argument in favor of routine exploration.

Another factor in favor of exploration is the ability to examine the sphincter of Oddi. This was found to be fibrotic in 8 instances

in the present series. While difficult to evaluate per se, it is to be noted that this lesion led to the necessity for a second operative procedure in 1 of our patients who had previously had a cholecystectomy alone. Narrowing of the sphincter will not always result in symptomatic biliary disease, however, and interpretation of such narrowing is subjective. Therefore, these figures are excluded from the "positive" results of exploration.

The use of antibiotics in our series may have reduced the incidence of recognized morbidity. In 97 instances antibiotics were not used, and in 36 patients (37 per cent) a morbid condition developed. In 250 instances, antibiotics were not indicated but were used as a prophylactic measure, and in 65 patients (25 per cent) complications developed. And if complications related to the presence of the T tube are eliminated from this comparison—because no such complication can occur in the first group—the figures become 53 out of 250 or 21 per cent. The protective value of antibiotics is suggested by examination of the group of patients in whom bacterial contamination was likely or present. This group of 99 patients had a morbidity rate of 25 per cent—no higher than the treated "clean" cases, and lower than the "clean" cases untreated with antibiotics.

Comparison of group morbidity (Table II) shows that procedures associated with common duct exploration (groups II and III) are associated with a higher morbidity rate than without exploration (groups I and IV). However, when the complications which occur because of the T tube per se are subtracted, one finds that in only 63 of 249 cases (groups II and III together) did a morbid state develop, a percentage (25 per cent) which is identical to that of the unexplored groups. Such figures indicate that the antibiotic statistics do not relate to the underlying disease nor to the extent of operation, but do relate to the factor of incision alone.

The comparison of late complications to antibiotic use is interesting in that an 11 per cent rate followed when antibiotics were not used, whereas a 7 per cent rate occurred when they were used, despite "selection" of the more seriously ill patients in this latter group. This observation further suggests that antibiotics serve a useful purpose in the postoperative care of biliary tract procedures. Nevertheless, the occurrence of 9 incisional hernias in antibiotic-treated patients illustrates that operative technique is still paramount.

CONCLUSIONS

1. The discovery of clinically silent choledocholithiasis is desirable. This can be accomplished with least effect on morbidity and mortality by operative roentgenologic investigation.

2. The postoperative use of antibiotics may reduce the early and late morbidity without respect to such factors as recognized bacterial contamination and likelihood of infection.

SUMMARY

The 5 year experience with biliary tract operations at the University of Kansas is reviewed. Postoperative duration was lengthened by 3.5 days when choledochostomy was added to cholecystectomy. A "yield" of 3 per cent of unsuspected cases of choledocholithiasis resulted from operative exploration of the common duct; whereas roentgenologic exploration yielded 6 per cent without affecting the morbidity or mortality. Use of antibiotics, whether prophylactic or indicated, was associated with a decreased early and late morbidity as compared with untreated, clean cases.

REFERENCES

1. Colcock, B. P. Operative Procedures on the Gallbladder and Common Duct; Surgical Practice of the Lahey Clinic. Pp. 469–478. Philadelphia: W. B. Saunders Co., 1951.
2. Langenbuch, Carl. Ein Fall von Extirpation der Gallenblase wegen chronischer Cholelithiasis, Heilung. Berl. klin. Wschr., 1882, 19: 725–727.
3. Leichtling, J. J., Rubin, S., and Breidenbach, L. The significance of in vivo measurements of the common bile duct. Surg. Gyn. Obst., 1959, 109: 773–777.

AN ANALYSIS OF FACTORS WHICH INFLUENCE MORTALITY FOLLOWING EXTENSIVE ABDOMINAL OPERATIONS UPON GERIATRIC PATIENTS

LEROY H. STAHLGREN, M.D., F.A.C.S., Philadelphia, Pennsylvania

THERE IS A CONTINUING NEED to analyze and to measure the risks which are associated with geriatric surgery. Most workers have reported an increased mortality rate after operation on patients over 69 years of age when compared to younger patients (Table I). Brooks reported that it was the disease and not the operative treatment which was responsible for the increased mortality. He stated that ". . . deaths which could be reasonably attributed to operative treatment were remarkably infrequent" in his experience. Welch recorded a mortality rate of 20.7 per cent in 129 patients who had undergone extensive abdominal surgery. He believed that the seriousness of the patient's disease was the principal cause of the high mortality rate. Gastrointestinal cancer occurred in 39.9 per cent of this group, and only 40 per cent of the lesions were resectable. In Gilchrist's and de Peyster's series of 99 patients, 23 per cent were found to have fatal diseases such as carcinomatosis or late intestinal obstruction with peritonitis. Among Rankin's and Johnston's patients, 54.5 per cent had cancer; one-third of the lesions were nonresectable. Haug and Dale contended that the exclusion of patients who were already doomed by the disease process considerably decreased geriatric mortality rates.

The influence of age and its associated degenerative changes on the mortality rate of geriatric patients has been interpreted in conflicting ways. Gilchrist and de Peyster concluded that neither age nor chronic cardiovascular, pulmonary, or renal disease had any effect on the mortality rate in their series of 189 patients. Mithoefer and Mithoefer postulated that the increased mortality rate in elderly patients was not dependent on old age itself. In their patients, arteriosclerotic heart disease and chronic pulmonary disease were as common in the patients who survived operation as in those who died. They believed that it was the intolerance of the elderly to postoperative cardiorespiratory complications and to misdirected therapy that caused the increased mortality. On the other hand, Cole (6) stated that, in his experience, concurrent and complicating diseases elevated the mortality rate after extensive operations in elderly patients. He stressed the importance of the physiologic differences between young and old (7).

Anglem and Bradford incriminated the aging process and accompanying medical diseases as the cause for increased mortality in elderly people. These workers believed that physiologic changes in the aged caused diminished cardiac, pulmonary, and renal reserves, lowered vital capacity, and decreased metabolic rate. Parsons and Purks (23) blamed the lack of physiologic reserve for the inability of patients in the older age groups to tolerate the consequence of errors in surgical technique.

Carp and Meyer and associates have referred to the increased incidence and higher mortality rate which follow emergency operations when compared to elective procedures in geriatric patients. Welch stressed the importance of early diagnosis and planned operation in preventing the high mortality of emergency surgery. It has also been pointed out that aged patients do not tolerate infec-

From the Philadelphia General Hospital, Philadelphia.

TABLE I.—MORTALITY RATE AFTER EXTENSIVE ABDOMINAL SURGERY

Author	*Year*	*Minimum age, yrs.*	*No. of patients*	*Operative mortality, per cent*
Welch.....	1948	70	140	20.0
Childs and Mason	1948	70	99	17.2
Oberhelman.....	1953	70	139	8.6
Anglem and Bradford.....	1953	70	443	11.5
Herron, Jesseph, and Harkins..	1960	70	565	21.6
Stahlgren.....	1961	70	102	15.3

tions, intestinal obstruction, and chronic diseases as well as do younger patients. Bosch and co-workers held that concurrent disease, hypertension, and arteriosclerosis doubled the mortality rate in patients over 60 years of age.

Nachlas and associates stated that the postoperative mortality rate among patients with arteriosclerotic heart disease is 2 to 3 times higher than the average. They concluded that the increased risk of surgery in the aged was due in large part to the presence of arteriosclerotic heart disease. Morrison believed that there was a relationship between operative mortality and coronary artery disease. Dry, Ernsterne, and Etstein and Hannigan and their associates have reported that operative risk was not increased, or increased only slightly, in a patient with coronary arteriosclerosis who can carry on moderate physical activity. Certain of the cardiac defects resulting from coronary artery disease have been studied to evaluate their effect on mortality rate. Weiss and Weiss reported 50 patients ranging from 46 to 86 years of age who had suffered a myocardial infarction at least 4 weeks earlier; the mortality rate due to cardiac complications was 9.4 per cent. They referred to previous articles reporting a total of 253 operations in patients of all age groups with healed myocardial infarcts with a mortality of 5.1 per cent. They concluded that the operative risk was slightly greater than that expected in a comparable group of patients without heart disease. Finkbeiner and associates reported a 5 per cent mortality rate after major operations on patients with chronic auricular fibrillation. They believed that adequately treated chronic auricular fibrillation, per se, did not increase morbidity or mortality. Pfeiffer and LaDue studied 59 patients with bundle-branch block who underwent extensive operations with a mortality of 3.3 per cent due to cardiac complications. They concluded that bundle-branch block was associated with a higher risk; the increase could be kept at a minimum by meticulous management. Gertler and associates reported 56 elderly patients with bundle-branch block who underwent extensive operations without death.

It is apparent that no simple formula has been found which will assure the successful surgical management of aged patients. However, attempts have been made to develop principles which would provide a safe approach to geriatric surgery. Rankin and Johnston stated that "The nicety of surgical judgment as to when, what, and how much to do is the keynote to success in these patients." Welch advised that all measures found useful in the safe conduct of the adult surgical patient be intensified in their application to the elderly. Haug and Dale believed that the principles of management of aged patients do not differ essentially from those used for younger patients. However, they recommended close attention to details to prevent further loss of the aged patient's decreased functional reserve. This view has been supported by Meyer and associates and Stewart and Alfano. Gilchrist and de Peyster listed 7 modifications of surgical care to serve as safeguards. Raven stated that the simplest operation should be performed that will cure the condition causing symptoms.

It is interesting to note that the terms "diminished physiologic reserve" and "decreased functional reserve" have not been satisfactorily defined, nor have they lent themselves to clinical measurement.

CLINICAL DATA

One hundred two consecutive patients over 69 years of age who underwent 111

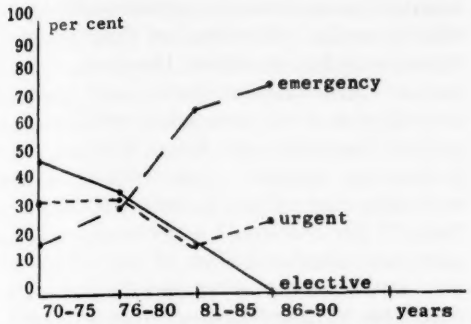


FIG. 1. Influence of age on incidence of elective, urgent, and emergency cases.

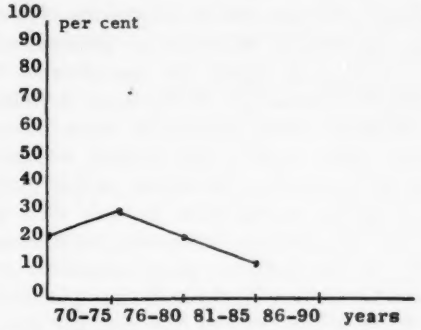


FIG. 2. Influence of age on mortality rate in nonelective cases.

extensive abdominal operations were reviewed for two reasons: first, to identify those factors which increased the mortality rate when compared to that in younger patients; and, second, to evaluate the effectiveness of measures which were used to decrease the mortality rate. All patients were treated at a large general hospital during a period of 1 year. The care of each patient was the responsibility of the author; most of the surgical procedures were performed by residents. Gynecologic, urologic, and orthopedic procedures were excluded. Thirty-six operations were performed on the colon and rectum; 9 on the biliary tract; 12 on the stomach; and 4 on the small intestine, for obstruction. There were 46 herniorrhaphies; 2 appendectomies were performed; and there were 2 miscellaneous procedures.

Patients who were discharged from the hospital are listed as survivors, although they may have succumbed from their disease at home. Patients who died during hospitalization, even after prolonged periods, are listed as deaths. Eighty-five patients survived operation, and 17 died. The patient mortality was 16.7 per cent; the operative mortality was 15.3 per cent.

EVALUATION OF FACTORS WHICH INFLUENCED OPERATIVE MORTALITY RATE

Age. The patients' ages ranged from 70 to 94 years. With increasing age, the frequency of elective operations decreased (Fig. 1). Very few elderly patients were refused indicated elective surgery; therefore, the decreased incidence of elective surgery in the older age groups was due to circumstances existing outside the hospital. Case selection did not occur in patients with urgent or emergency indications for operation. Therefore, the mortality rate that followed nonelective surgery is a significant measure of the relative surgical risk in various age groups. Since the mortality rate after nonelective procedures did not increase with advancing age, it is apparent that chronologic age, in itself, did not affect the mortality rate (Fig. 2).

Advanced stage and serious nature of the primary disease. Because of the preponderance of indigent patients in the hospital population, far advanced and incurable diseases were commonly encountered. Some of the patients were insane. Most were malnourished and underweight. One-third of the operations were emergencies. The mortality rate after emergency surgery was 2½ times higher than the mortality rate after nonemergency surgery. After 34 urgent operations, 8 patients died, a mortality of 23.5 per cent. Nine of 36 patients undergoing emergency operations died, a mortality of 25 per cent. The 111 procedures resulted in 94 survivors and 17 deaths, an over-all mortality of 15.3 per cent.

Operations for gastrointestinal cancer comprised 38.7 per cent of the total and re-

sulted in 82 per cent of the deaths. The remaining deaths occurred in patients who were operated upon for complicated intestinal obstruction. Forty-three definitive procedures were performed upon 37 patients with cancer; the patient mortality was 37.8 per cent. Resection of the malignant lesion was possible in only 48.6 per cent of the patients. Extensive local metastasis or the patient's poor condition prevented resection in the remaining patients. In most of the cases of resection the operation was not curative because of the existence of distant metastases.

Appendicitis was an uncommon disease in this series. Two appendectomies were performed and there was no death. In each case the pathologic changes were far advanced.

Coexisting degenerative diseases. Pre-existing degenerative diseases were identified and listed under the appropriate system during the preoperative workup. Only those serious physical abnormalities were included which exceeded the expected degenerative or arteriosclerotic changes.

One hundred seventy-nine serious physical defects were discovered in 83 patients. Fifty-six positive findings were recorded in the cardiovascular system; 44 in the respiratory system; 41 in body fluids—blood volume in 35, electrolytes in 6; 17 in the genitourinary tract; 12 in veins of the extremities; 4 in the liver; and 5 in miscellaneous parts of the body. There were no positive findings in 19 patients. The mortality rate was 18 per cent in the former group, and 10.5 per cent in the latter group.

There were 56 serious cardiovascular problems in 43 patients; the mortality rate was 16.2 per cent (Table II). Most of the patients who died were found to have degenerative changes involving other systems. Two or more cardiovascular abnormalities were demonstrated in 7 patients. Only 1 of these patients died. The remaining 59 patients showed no particular cardiac defect; the mortality rate was 16.9 per cent. There was no difference in the over-all mortality rates between patients with identifiable cardiac disorders and those without obvious cardiac disorders. However, hypertensive cardiovascular disease and cardiac arrhythmias were associated with an increased mortality rate. When deaths due to irreversible disease were excluded, the mortality rate of the former was reduced from 25 per cent to 16.6 per cent, and the latter was decreased from 25 per cent to 10 per cent. Likewise, when deaths due to irreversible primary disease were excluded, the mortality rate of patients without these two cardiac abnormalities was 4.3 per cent. The presence of congestive heart failure, after proper treatment, did not increase the mortality rate. Eleven patients with congestive heart failure were operated upon, after correction of the cardiac decompensation, without a death. The presence of a healed myocardial infarction did not increase the mortality rate.

An 80 year old man was admitted with acute perforation of a benign gastric ulcer. The following preoperative abnormalities were discovered: marked anemia and hypovolemia probably due to blood loss from the peptic ulcer; congestive heart failure due to arteriosclerotic heart disease; and bilateral bronchopneumonia. The preparation for emergency operation consisted of the following measures: transfusion of 1,500 cubic centimeters of whole blood; rapid intravenous digitalization; tracheal aspiration; and institution of treatment with antibiotics. The operation consisted of patching of the ulcer. The postoperative convalescence was uneventful. The identification and treatment of congestive failure improved cardiac function and permitted safe abdominal operation.

There were 44 serious preoperative abnormalities of the respiratory system in 29 patients; the mortality rate was 17.2 per cent. This did not differ significantly from the mortality rate of 16.4 per cent in the patients without respiratory diseases. Eighty per cent of the patients with preoperative pulmonary disorders who died after operation had defects involving other systems. The respiratory diseases included: 21 instances of emphysema; 10 of pneumonia; 4 of bronchiectasis; 2 of bronchitis; 1 of empyema; 4 of pulmonary fibrosis; and 2 other defects.

Seventeen patients showed serious urinary tract disease; the mortality rate was 29.4 per cent. The mortality rate in patients without urinary tract disease was 16.4 per cent. All of the patients who died had from 1 to 4 serious defects of other systems. The urinary tract diseases consisted of cystitis, chronic pyelonephritis, and obstruction due to prostatic enlargement. Septicemia caused by unrecognized chronic renal infection was fatal in 2 cases.

Varicose veins and phlebitis of the lower extremities were discovered in 12 patients; the mortality rate was 8.3 per cent. This figure is lower than the mortality rate of 17.8 per cent for patients without venous disease. The 1 death occurred in a patient with diseases affecting 4 other systems and was unrelated to the venous disease.

Impaired liver function was noted in 4 patients; none died.

Depletion of body fluids. Thirty-five patients had serious hypovolemia; the mortality rate was 28.6 per cent. In most instances, abnormalities coexisted in other systems. Blood volume measurement was used selectively. Whole blood or packed red cells were administered, depending on the deficit.

An 85 year old man was admitted with the diagnosis of carcinoma of the sigmoid. The following findings were recorded: moderate anemia, as evidenced by a hemoglobin value of 9.5 grams; arteriosclerotic heart disease with auricular fibrillation; and moderate pulmonary emphysema. The blood volume was slightly reduced to 3.9 liters from a calculated normal of 4.3 liters. The anemia and hypovolemia were corrected by the administration of packed red cells. Digitalis was used to control the auricular fibrillation. Anterior resection of the sigmoid colon was performed after preparation of the bowel with sulfathalidine. Postoperative tracheal aspirations were carried out. Convalescence was uneventful. Correction of the anemia without overloading the circulation was successfully performed by using packed red cells.

Six patients with severe electrolyte and acid-base imbalance were encountered; deficiencies were corrected in all patients preoperatively. There were no deaths.

Anesthesia. Local infiltration or regional block anesthesia was used in 15 patients. There were 3 deaths, but all were the result of irreversible disease rather than the anesthetic or operative procedure.

TABLE II.—PROGNOSTIC SIGNIFICANCE OF PREOPERATIVE CARDIAC DEFECTS

Cardiac diagnosis	*No. of times each diagnosis occurred*	*Mortality rate for each diagnosis, per cent*	*Mortality rate after exclusion of unavoidable deaths, per cent*
Arrhythmia.....	20	25	10
Hypertensive cardiovascular disease.....	12	25	16.6
Congestive failure	11	0	0
Myocardial infarction, old...	10	10	0
Cardiac hypertrophy, no cause determined....	3	0	0
Total.....	56	16.2	9.3

A 79 year old man was admitted with a left indirect inguinal hernia. The preoperative evaluation revealed severe hypertensive arteriosclerotic heart disease, a history of congestive failure, and evidence of an old myocardial infarct. Elective hernia repair was carried out under local anesthesia. The postoperative course was uneventful. The greatest risk to this patient would have been a period of anoxia or hypotension during general or spinal anesthesia. Local anesthesia may be used in such situations and is entirely satisfactory.

The majority of patients were given spinal or endotracheal inhalation anesthesia. A detailed discussion of the anesthetic management of geriatric patients will appear in another report.

Type of operation. The magnitude of the operative procedure did not always influence the mortality rate. This fact is demonstrated by the outcome of 14 gastric operations: 12 gastric resections were performed for peptic ulcer disease without a death, whereas 2 palliative gastroenterostomies for cancer were followed by death. The deaths resulted from the patient's disease rather than the operative procedure. There were no deaths after elective repair of 31 hernias; but there was a mortality rate of 9 per cent for 11 patients with incarcerated hernia, and 25 per cent for 4 patients with strangulated hernia. It is evident that the extent of the disease was more significant than that of the operation. However, operations were carried out in multiple stages

whenever the patient's condition would not permit a one stage procedure. Three stage operations for colon obstruction were performed in 5 poor risk patients; there was no mortality associated with these 15 procedures. Bilateral hernias were usually repaired in 2 stages separated by an interval of 7 to 10 days.

Postoperative complications. Twenty-one patients suffered 28 serious postoperative complications with a mortality rate of 61.9 per cent: 10 instances of respiratory complications with a mortality rate of 77.7 per cent; 7 of wound infections with a 42.8 per cent mortality rate; 6 of cardiovascular complications with an 83 per cent mortality rate; all 3 patients with septicemia died; and of 2 patients with intestinal obstruction, 1 died. Only 8 patients recovered from major complications. Four patients, in addition to these, died immediately after emergency surgery; no particular complication could be identified. The remaining 77 patients recovered without complication. The 7 patients whose deaths are listed as avoidable suffered 13 major complications.

Six major cardiovascular complications occurred; congestive failure in 3 patients; acute myocardial infarction in 2; and auricular fibrillation in 1 patient. Five patients died; the mortality rate was 83.3 per cent. The death was attributed directly to the cardiac complication in 3 patients and was indirectly related in 2. Two of the 3 patients whose deaths resulted directly from cardiac complications did not show a cardiac disorder preoperatively.

Ten postoperative respiratory complications occurred in 9 patients; the mortality rate was 77.7 per cent. The complications consisted of pneumonia, 8 cases, with a mortality rate of 71.4 per cent, and 2 cases of pulmonary emboli, with a mortality rate of 100 per cent. Neither of the latter patients showed preoperative venous disease. In 1 of them minimal discomfort in the calf of the leg developed the same day the embolism occurred. In 5 patients, or 17.2 per cent of those with preoperative respiratory disease, postoperative respiratory complications developed.

DEATHS

The major causes of death were cardiovascular in 6 patients; sepsis in 3; respiratory in 3; renal in 1; and carcinomatosis in 4.

Avoidability of death. In retrospect, it appears that errors were committed in the surgical care of 7 of the 17 patients who died. In the remainder the primary disease was irreversible. Whereas every error may not have significantly influenced the final result, careful scrutiny of each mistake may help us to prevent their recurrence.

The major errors are summarized as: (1) preoperative preparation—misinterpretation of a normal hemoglobin value to represent evidence of a normal blood volume; (2) operation—treatment of hypovolemic shock with vasopressors rather than blood; technical mismanagement of operative hemorrhage with delayed control of blood loss; creation of a transverse colostomy for perforated sigmoid carcinoma when a sigmoid colostomy would have achieved more complete decompression; and (3) postoperative care—unrecognized urinary tract infection which led to septicemia; failure to detect signs of phlebitis in the leg before appearance of a massive pulmonary embolism; prolonged conservative treatment of postoperative intestinal obstruction when operative intervention was necessary.

DISCUSSION

A careful review of a group of indigent patients, many of whom had far advanced systemic and visceral defects, is of value because it permits the assessment of those defects which may occur in a lesser degree in any geriatric patient. Allen has called attention to the differences between the results which should be expected in the treatment of indigent and of private patients. He concluded that surgical treatment of the indigent patient carries a much higher mortality and is followed by more complica-

tions than is surgical treatment of the financially secure patient. Whereas it is true that the problems encountered in both groups differ quantitatively, the problems are qualitatively the same. Therefore, those factors which affected the mortality in this series merit further comment. It is apparent that chronologic age did not influence the mortality rate in this series. Therefore, age, in itself, should not be considered a contraindication to surgical treatment.

The over-all operative mortality rate in this series would have been reduced if needed operations had been planned at a time of election before the disease had progressed to an advanced stage. Therapy proved to be hopeless because of irreversible disease in 58.9 per cent of the patients who died; by the most critical analysis, 41.1 per cent of the deaths could be considered avoidable. This is comparable to the figure of 30 per cent reported by Mithoefer and Mithoefer in their series of geriatric patients. One must conclude, therefore, that the best possible care of the patients in this series could not have reduced the mortality rate below 9.9 per cent, which represents the unavoidable deaths. This obligatory increase, resulting from irreversible disease, is the major factor in the increased mortality of aged patients when compared to younger patients.

However, the magnitude and the advanced state of the disease and the accompanying constitutional changes do not account for all the hazards of geriatric surgery. The degenerative changes increased the surgical risk but very few of them increased the mortality rate in this study. Hypertensive cardiovascular disease, when associated with changes in the heart, kidneys, and brain proved to be the most serious preoperative defect because of the narrow margin of safety which exists in these patients. Their capacity to adjust to transient anoxia or hypotension during induction of anesthesia and to operation or a postoperative complication is gravely impaired. Insofar as cardiac arrhythmia was an indication of coronary artery disease and an ischemic heart, there was also a higher mortality rate in this group. It is interesting to note that none of the other cardiovascular abnormalities encountered in this study affected the mortality rate. Patients with electrocardiographic and clinical evidence of a healed myocardial infarction and patients with properly treated cardiac decompensation proved to be safer risks than patients without a preoperative cardiac disorder. The absence of identifiable preoperative cardiac abnormalities did not insure that fatal postoperative cardiac complications would not develop. The relative safety with which many patients with cardiac defects tolerated operation may be due partly to accurate preoperative diagnosis and treatment of the defects. Ochsner's often quoted observation that cardiac patients are safe for operation because they are regarded as especially unsafe may substantiate this assumption, according to Parsons and associates (24). Patients with congestive failure and chronic auricular fibrillation, or patients with borderline or incipient failure, on whom an extensive procedure was planned, were digitalized. Digitalis was not used prophylactically.

The majority of patients showed pulmonary emphysema; some had associated chronic bronchial infection. Such patients and those with marked respiratory disorders listed previously were operated upon with a low mortality rate. These results were partly the outcome of aggressive preoperative treatment of the respiratory diseases. Drainage of retained bronchial secretions and efforts directed toward increasing pulmonary ventilation were considered most important; the patient was encouraged to cough and to be ambulatory when possible. Tracheal aspiration and bronchoscopy were infrequently necessary. Intermittent positive pressure breathing was rarely used but is a useful tool and could have been utilized more frequently. Antibiotics were given whenever pulmonary infection was present.

Postoperative respiratory complications were usually fatal. They often initiated a chain of complications which led to the patient's death. For this reason, preventive measures were considered to be most important. Patients who were capable of a reasonably effective cough postoperatively were encouraged to do so at frequent intervals. Many were subjected to repeated tracheal aspirations to initiate forceful coughing. In a few instances, tracheotomy was performed to aspirate thickly purulent material if present in great quantity. Atelectasis was prevented by encouraging or causing marked respiratory excursions; this resulted in effective pulmonary ventilation. Appropriate antibiotics were used whenever a pulmonary complication occurred.

Impaired renal function due to nephrosclerosis was not, in itself, a serious problem. Such patients exhibited azotemia and low urinary specific gravity but tolerated operation well if the fluid and electrolyte therapy was well managed. However, when these changes were associated with far advanced arteriosclerotic disease in the heart and brain or with chronic pyelonephritis, operation proved to be hazardous. Urinary obstruction due to prostatic disease was serious only if unrecognized. An indwelling catheter was used in these patients during the early postoperative period.

The most efficient function of the heart, lungs, kidney, and brain was obtained by preoperative replacement of blood volume and fluid deficiencies. A normal oxygen supply is needed by these organs which, because of arteriosclerotic and degenerative changes, are unable to compensate for the added strain of operation. Appropriately used blood transfusion is a most important adjunct to preoperative care of the geriatric patient, according to Hero and Barber. This is one circumstance in which the benefit from a single unit of blood far outweighs the risk of transfusion reaction. Prophylactic therapy of patients with peripheral venous disease successfully prevented postoperative pulmonary emboli in this study. These results suggest that venous disease, when recognized and properly treated preoperatively, does not increase the mortality rate. Elastic leg wrappings were applied when varicose veins were present. Ambulation was encouraged. Patients with active thrombophlebitis were treated with anticoagulant drugs and bed rest until the process had subsided. In a few instances, when emergency surgery was carried out despite the presence of phlebitis, anticoagulant therapy was used postoperatively.

CHOICE OF OPERATIVE PROCEDURE

Usually the best procedure for a young patient is also the best choice for aged patients. Furthermore, meticulous technique should be common to surgery in both groups. There are circumstances, however, in which procedures of less magnitude will accomplish the same purpose with less risk than more extensive procedures. In this regard, efforts should be directed toward returning the geriatric patient to comfort and to gainful independence. The operation chosen should be the one which adequately accomplishes this purpose and which is accompanied by the least anesthetic and operative trauma. Efforts to achieve long term or permanent cures with very radical operations might well be reserved for younger patients.

An 83 year old woman was admitted with the diagnosis of upper gastrointestinal hemorrhage. The following abnormalities were discovered: anemia, represented by a hemoglobln of 10 grams; severe arteriosclerotic heart disease with congestive failure and evidence of an old myocardial infarction; pulmonary emphysema; and bilateral bronchopneumonia. After 7 units of whole blood, rapid intravenous digitalization, and institution of antibiotic therapy, laparotomy was performed. A prepyloric gastric erosion was identified by gastrotomy as the source of bleeding. The erosion was locally excised and a pyloroplasty and vagotomy were performed. Tracheal aspiration was carried out and antibiotics were given postoperatively. Convalescence, without further bleeding, was uneventful. The least traumatic and shortest operative procedure to control the hemorrhage was performed.

Ziffren believes that 2 or 3 staged procedures are better tolerated in the depleted

patient than a single operation of greater extent. In this series the staging of operations was successfully followed in all patients with colon obstruction due to neoplasm and in certain poor risk patients with complicated acute cholecystitis in whom cholecystectomy would have been technically difficult. Local anesthesia was frequently utilized for the initial decompressive procedure, i.e., colostomy or cholecystostomy.

SUMMARY AND CONCLUSIONS

Factors which increased the mortality rate were:

1. Emergency operation. The mortality rate was 2½ times higher for emergency operations than for nonemergency procedures.

2. Serious nature and advanced stage of the patient's disease. Eighty-two and one-half per cent of the deaths in this series occurred in patients with far advanced cancer; the remaining deaths occurred in patients with far advanced intestinal obstruction. Any comparison of mortality statistics between young and old patients must take into account the obligatory increase in mortality rate in the elderly due to the high incidence of irreversible disease. The average geriatric patient will survive abdominal procedures, however.

3. Concurrent degenerative diseases. The degenerative systemic effects of aging increase surgical risk, but, in this study, only certain of them increased the mortality rate. Hypertensive cardiovascular disease and cardiac arrhythmias were associated with a corrected mortality rate of 15 and 10 per cent, respectively, as compared with an over-all mortality rate of 4.3 per cent. The worst risks were those patients who had generalized arteriosclerotic changes which affected the function of the heart, kidneys, lungs, and brain.

4. Postoperative complications. Serious cardiorespiratory complications were associated with a 75 per cent mortality rate.

5. Errors in preoperative preparation, operative technique, choice of operation, and recognition or treatment of complications. Errors were detected in 40 per cent of the patients who died. The remaining deaths resulted from the primary disease. Chronologic age, in itself, did not influence mortality rate.

Measures which decreased the mortality rate were:

1. Planned, elective operation. There were no deaths after elective surgery.

2. Identification and correction of preoperative physical defects as follows: Correction of hypovolemia and fluid and electrolyte deficiencies; digitalization of the decompensated or fibrillating heart; increased pulmonary ventilation and bronchial drainage; use of antibiotics in the presence of infection; use of an indwelling catheter for prostatic urinary obstruction; ambulation, leg wrapping, and prophylactic anticoagulants for obvious venous disease of the lower extremities.

3. Expert anesthesiologist. Occasionally local anesthesia was used.

4. Choice of the shortest and least traumatic operative procedure to correct the patient's most threatening disorder.

5. Prompt recognition and treatment of postoperative complications, particularly sepsis, intestinal obstruction, and pulmonary complications.

The average geriatric patient will survive extensive abdominal procedures, but the simplest operation that will correct his condition is recommended. A goal of the surgical treatment of geriatric patients should be the dissociation of increased surgical risk from increased surgical mortality. A better understanding and method of clinical measurement of the endocrinologic, nutritional, and functional differences between young and old patients will be helpful in accomplishing a decrease in surgical mortality.

REFERENCES

1. Anglem, T. J., and Bradford, M. L. Major surgery in the aged. J. Am. M. Ass., 1953, 249: 1005.
2. Bosch, D. T., Islami, A., Tan, C. T. C., and Beling, C. A. The elderly surgical patient. Arch. Surg., 1952, 64: 269.

3. Brooks, B. Surgery in patients of advanced age. Ann. Surg., 1937, 105: 481.
4. Carp, L. Mortality in geriatric surgery. Brit. M. J., 1950, 2: 1198.
5. Childs, P., and Mason, S. A. Surgical management of the aged. Brit. M. J., 1949, 2: 1389.
6. Cole, W. H. Operability in the young and aged. Ann. Surg., 1953, 138: 145.
7. Idem. Problems in operability. Bull. Am. Coll. Surgeons, 1955, 40: 41.
8. Dry, T. J. Reducing the risk of operations for the patient with cardiac disease. Surg. Clin. N. America, 1940, 20: 1169.
9. Ernsterne, A. C. The management of cardiac patients in relation to surgery. Circulation, 1951, 4: 430.
10. Etstein, B., and Proger, S. Operative risk in patients with coronary artery disease. J. Am. M. Ass., 1955, 159: 845.
11. Finkbeiner, J. A., Wroblewski, F., and LaDue, J. S. Major surgery in patients with chronic auricular fibrillation. N. York J. M., 1954, 54: 1175.
12. Gertler, M. M., Finkle, A. I., Hudson, P. B., and Neidle, E. G. Cardiovascular evaluation in surgery —I, operative risk in cancer patients with bundle branch block. Surg. Gyn. Obst., 1954, 99: 441.
13. Gilchrist, R. K., and de Peyster, F. A. Principles and safeguards in abdominal surgery of the aged. J. Am. M. Ass., 1956, 160: 1375.
14. Hannigan, C. A., Wroblewski, F., Lewis, W. H., and LaDue, J. S. Major surgery in patients with healed myocardial infarction. Am. J. M. Sc., 1951, 222: 628.
15. Haug, C. A., and Dale, W. A. Major surgery in old people. Arch. Surg., 1952, 64: 1.
16. Hero, B. A., and Barber, H. Blood volume in the elderly patient before and after surgery. Surgery, 1950, 27: 531.
17. Herron, P. W., Jesseph, J. E., and Harkins, H. N. Analysis of 600 major operations in patients over 70 years of age. Ann. Surg., 1960, 152: 686.
18. Meyer, K. A., Jacobson, H. A., and Beaconsfield, P. Surgical treatment of the octogenarian. J. Internat. Coll. Surg., 1958, 29: 263.
19. Mithoefer, J., and Mithoefer, J. C. Studies of the aged. Arch. Surg., 1954, 69: 56.
20. Morrison, D. R. The risk of surgery in heart disease. Surgery, 1948, 23: 561.
21. Nachlas, M. M., Abrams, S. J., and Golberg, M. M. The influence of arteriosclerotic heart disease on surgical risk. Am. J. Surg., 1961, 101: 447.
22. Oberhelman, H. A. Surgical problems of the aged. J. Internat. Coll. Surg., 1954, 21: 458.
23. Parsons, W. H., and Purks, W. K. A report upon the elderly patient as a surgical risk. Arch. Surg., 1949, 58: 888.
24. Parsons, W. H., Whitaker, T., and Hinton, J. K. Major surgery in patients 70 years of age and over. Ann. Surg., 1956, 143: 845.
25. Pfeiffer, P. H., and LaDue, J. S. Major surgical operations in presence of bundle-branch block; study of operative risk in 59 patients. Am. J. M. Sc., 1949, 217: 369.
26. Rankin, F. W., and Johnston, C. C. Major operations in elderly patients. Surgery, 1939, 5: 763.
27. Raven, R. W. Surgery in octogenarians. Brit. M. J., 1955, 1: 266.
28. Stewart, J. D., and Alfano, G. S. Surgery of the elderly. J. Am. M. Ass., 1954, 154: 643.
29. Weiss, M. M., Sr., and Weiss, M. M., Jr. Risk of major surgery in patients with old myocardial infarction. Surgery, 1959, 46: 1094.
30. Welch, C. S. Surgery in the aged. N. England J. M., 1948, 238: 821.
31. Ziffren, S. E. Reduction in operative mortality in the very aged. J. Am. M. Ass., 1953, 152: 994.

THE COAGULATION OF BLOOD IN ISOLATED VENOUS SEGMENTS

HECTOR M. MARIN, M.D., JANETTE LEMIEUX, and LISELOTTE MUELLER,

Boston, Massachusetts

BLOOD retains its fluid state within the intact vascular system for a lifetime, yet clots immediately when a vessel is severed. This most remarkable property of the blood, which has puzzled several generations of investigators, has not been totally elucidated. Several mechanisms co-operate in preserving the fluidity of the blood. Some of these are active in the blood itself; others are probably related to specific physiologic properties of the vascular wall. The liver certainly plays a major role in regulating blood coagulability because of its ability to synthesize coagulant substances as well as powerful anticoagulants.

In this study we propose to investigate the physiologic mechanism responsible for the fluidity of the blood in isolated venous segments. It is known that when two ligatures are properly applied around a vessel without injuring the intima, the blood contained within the occluded segment may remain fluid indefinitely or, at best, clots incompletely. If the mechanism responsible for this behavior is assumed to operate also in the entire vascular system, coagulation studies in isolated venous segments should then help to elucidate the mechanism responsible for the fluidity of the blood throughout the body.

MATERIALS AND METHODS

Experiments were carried out on 52 mongrel dogs weighing from 7 to 18 kilograms and kept under routine laboratory conditions. The animals were anesthetized with 20 milligrams per kilogram of intravenous nembutal. Both jugular and one of the femoral veins were exposed, and all the tributaries were carefully ligated. While the femoral vein was left intact, segments of both jugular veins were isolated between 2 nontraumatic vascular clamps applied 4 to 6 centimeters apart. The skin flaps were then loosely approximated on top of the veins with a few silk sutures. All the wounds were kept moist by periodic irrigations with isotonic saline solution.

Blood was obtained by venipuncture from the femoral vein at the beginning of the experiment for base line studies and from the occluded segments after 5, 10, 15, 20, and 30 minutes, and after 1, 2, 3, 4, 5, and 6 hours. Only 1 venipuncture was carried out in each vessel. Since the occluded segments, as a rule, did not contain more than 1 to 2 milliliters of blood, each specimen was limited either to plasma or serum. All plasma samples were collected in silicon-coated glassware. A volume of 0.2 molar sodium oxalate solution, equal to one-tenth of the amount of blood presumably present within the segment, was aspirated into a silicon-coated syringe prior to the collection of the plasma. Any blood in excess was discarded in order to keep the proportion between blood and anticoagulant constant.

The following coagulation studies were carried out on these samples.

Thromboplastin generation test. The generation of thromboplastin was studied by the method of Biggs and Douglas (5). The plasma from one of the jugular veins was allowed to react with the serum from the contralateral jugular vein. Since both specimens were collected at the same time, the results are presumed to be reliable. Cephalin, prepared by the method of Bell and Alton,

From the Surgical Laboratory of St. Elizabeth's Hospital and Department of Surgery, Tufts University Medical School, Boston.

TABLE I.—THE GENERATION OF THROMBOPLASTIN IN ISOLATED VENOUS SEGMENTS

Incubation time of the generation mixture, mins.	*General circulation*	*Isolated segments — Times after interruptions of blood flow*				
		30 mins.	*1 hr.*	*2 hrs.*	*4 hrs.*	*6 hrs.*
		Seconds				
(a)						
1	34.4	29.6	26.4	35.6	52.4	75.4
3	18.2	17.4	13.5	16.4	26.5	49.6
5	11.7	12.5	10.2	13.2	18.3	41.2
7	14.5	16.6	17.4	19.6	16.4	46.4
9	18.4	17.8	21.6	24.8	19.6	59.6
11	27.2	32.4	38.4	33.2	32.7	102.5
(b)						
1	32.4	29.2	34.3	35.5	71.6	124.5
3	16.2	12.4	14.5	16.6	52.7	96.2
5	11.4	13.5	15.7	16.2	45.1	87.4
7	14.8	18.4	21.8	24.7	38.4	72.8
9	23.9	24.7	24.2	32.8	64.1	104.1
11	31.4	38.5	32.6	46.9	96.5	139.1
(c)						
1	29.4	17.6	14.5	18.1	16.5	17.6
3	14.6	11.2	9.7	11.4	9.6	10.3
5	16.5	8.4	12.5	8.2	11.4	9.4
7	19.7	14.6	21.4	15.4	17.6	18.6
9	28.1	25.7	31.6	28.4	21.7	27.5
11	32.7	38.9	42.2	35.6	32.5	36.2

All data represent the average of 3 determinations.
(a) Plasma and serum from experimental animal.
(b) Normal serum and plasma from experimental animal.
(c) Normal plasma and serum from experimental animal.

was used as a platelet substitute in all these experiments. Plasma was diluted 1 to 25 and serum 1 to 10 in veronal buffer.

Hageman factor and plasma thromboplastin antecedent. The combined activities of Hageman factor and plasma thromboplastin antecedent were studied with the following method. Plasma was collected carefully in silicon-coated test tubes and treated with 100 milligrams per milliliter of barium sulfate. After 10 minutes' agitation at room temperature, the suspension was centrifuged and the supernatant transferred to another silicon-coated test tube and heated at 56 degrees C. for 30 minutes. With this procedure all the known clotting factors are destroyed with the exception of Hageman factor and plasma thromboplastin antecedent. After additional centrifugation for 10 minutes, 0.1 milliliter of the supernatant plasma was incubated at 37 degrees C. with 0.1 milliliter of citrated platelet-poor plasma and 0.1 milliliter of cephalin, and the clotting time of the mixture was determined after addition of 0.2 milliliter of 0.025 molar calcium chloride.

Plasma thromboplastin component and antihemophilic globulin. These two factors were studied by the cross-correction technique, using plasmas obtained from patients suffering from severe forms of Christmas disease or hemophilia. The clotting times thus obtained were converted to percentages of activity by means of a dilution curve.

Platelets and platelet factor 3. Platelet counts were carried out with a standard technique described by Stefanini and Dameshek. To determine platelet factor 3 activity, the plasma was heated at 60 degrees C. for 10 minutes, a procedure which destroys all the factors which play a role in the generation of thromboplastin, with the exception of platelet factor 3. Zero and one-tenth milliliter of the plasma thus treated was then incubated at 37 degrees C. with citrated platelet-poor plasma and the clotting time of the mixture was determined after addition of 0.2 milliliter of 0.025 molar calcium chloride.

Prothrombin. Prothrombin activity was determined in plasma with the method of Quick and by the following modification. A prothrombin-free substrate was prepared by

mixing 2 parts of barium sulfate-treated bovine plasma and 1 part of human serum. Serum was obtained from blood which was allowed to clot in the presence of a weak solution of rabbit brain thromboplastin to assure maximal consumption of prothrombin. This mixture of barium sulfate-plasma and serum contains in optimal amounts all the coagulation factors with the exception of prothrombin. Zero and one-tenth milliliter of the plasma under investigation, diluted 1 to 20 in veronal buffer, was incubated with 0.1 milliliter of the prothrombin-free substrate and 0.2 milliliter of permaplastin. The resultant clotting times were converted to percentages of activity by means of a dilution curve.

Factors acting on the conversion of prothrombin. Labile factor, factor 5, was studied with the method of Wolf (18). The activity of accelerators of the conversion of prothrombin to thrombin in plasma or serum was also determined by a previously published method (9). Barium sulfate-treated plasma or native serum, diluted 1 to 80 in veronal buffer, was incubated at room temperature with purified canine prothrombin and permaplastin in equal proportions. After 1, 2, 4, 6, and 8 minutes of incubation, 0.1 milliliter aliquots of the incubation mixture were transferred to tubes containing 0.1 milliliter of a 1 per cent solution of bovine fibrinogen in veronal buffer. The clotting times thus obtained were converted to units of thrombin by means of a standardization curve.

The thrombin generation. The generation of thrombin was studied on platelet-rich plasma by the method of Pitney and Dacie.

Fibrinogen. Fibrinogen determinations were carried out by the method of Adamis.

Antithromboplastin and antithrombin. Antithromboplastin was studied with the method previously described (9). Antithrombin was determined as follows: Zero and one-tenth milliliter aliquots of serum were incubated in a series of test tubes with 0.1 milliliter of a thrombin solution containing 10 units of thrombin per milliliter. After 10, 30, and 60 minutes of incubation, 0.1 milliliter of a 1 per cent solution of bovine fibrinogen was added to each of the tubes and the clotting times were recorded. The prolongation of the clotting times after incubation was interpreted as expression of the antithrombin activity of the serum. The most significant results were obtained after 10 minutes of incubation.

The fibrinolytic system. The components of the fibrinolytic system were studied by the fibrin plate method of Mullertz and Astrup, as previously described by our group (17).

RESULTS

Some interesting observations were made by gross inspection of the occluded segments in situ. About 30 minutes after the interruption of blood flow, a "sedimentation" of the corpusculated elements of the blood to the most dependent part of the isolated venous segments became evident. In 1 hour this phenomenon was almost completed. At this time, with a suitable light arrangement, it was possible to see through the semitransparent wall of the vessel a net separation between the red corpusculated phase at the bottom and the yellow plasmatic phase at the top. During the second hour, discrete round masses appeared at times within the segments. Upon opening the vessel, these masses lysed rapidly when manipulated. Examined under the phase microscope, they appeared to be formed by a loosely arranged fibrin mesh. When the content of the vessel was poured into a glass container, the blood usually clotted within a few minutes. Beyond the fourth hour of the experiment, however, the clotting times became very long.

Coagulation studies on these blood specimens revealed the following changes.

The generation of thromboplastin (Table I). A moderate increase in the amount of thromboplastin generated in the blood from the occluded segments was noted after the end of the first half hour. This was followed by a rather drastic decline between the fourth and sixth hours. When the barium sulfate-treated plasma from the experimental ani-

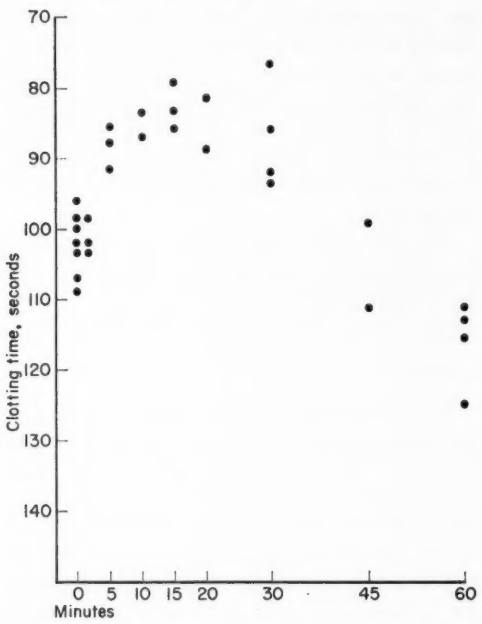


FIG. 1. Behavior of Hageman factor and plasma thromboplastin antecedent in isolated venous segments. A shortening of the clotting times is interpreted as the expression of increased activity. The first values at the left, time 0 on the abscissa, represent results obtained in blood from the general circulation in all the figures.

mal was incubated with normal serum, no definite trend was appreciable for at least 2 hours. Later there was a progressive decrease in both the speed and yield of thromboplastin generated. After 6 hours, the amount of thromboplastin generated did not exceed that formed when isotonic saline was added to the incubation mixture instead of plasma. Since the factors which play a role in the generation of thromboplastin in barium sulfate-treated plasma are antihemophilic globulin and labile factor, these results indicate a depletion of these factors within the occluded segments during the latter part of the experiment. When the serum from the experimental animal was incubated with normal plasma, a moderate increase in the generation of thromboplastin was noted. This is indicative of an increase in the activity of plasma thromboplastin component and Stewart factor.

The Hageman factor and plasma thromboplastin antecedent activity became elevated within the segments as early as 5 minutes after the initiation of the experiment, reached the climax in half an hour, and was exhausted after 1 hour (Fig. 1). Plasma thromboplastin component and antihemophilic globulin activity showed no change or, at best, moderate diminution during the first 15 minutes. Subsequently, an increase in plasma thromboplastin component and antihemophilic globulin was noted, the first preceding the second by about 10 minutes. After 4 hours their activity began to decline (Figs. 2 and 3). Plasma thromboplastin component activity was not eliminated by incubation at 37 degrees C. overnight. Antihemophilic globulin activity, on the other hand, was suppressed during storage or incubation at 37 degrees C. Furthermore, when antihemophilic globulin was determined on plasma treated with barium sulfate, a steady decline in activity was evident from the beginning of the experiment (Fig. 3). The discrepancy in activity of antihemophilic globulin, when measured in native plasma as compared to barium sulfate-treated plasma, indicates that antihemophilic globulin was consumed within the segments while new, more active intermediate products of the generation of thromboplastin were elaborated. These correct the defect of hemophilic plasma but have different chemical properties, since they are removed from plasma with the fraction absorbed by barium sulfate. Platelets showed only a moderate decrease for about an hour. Later they declined very rapidly and disappeared entirely from the segments in 4 to 5 hours (Fig. 4). The disappearance of platelets was accompanied by a concomitant rise in platelet factor 3 activity (Fig. 5).

Prothrombin. Prothrombin activity, when measured by the method of Quick, showed a rise at the beginning of the experiment. This lasted for about 2 hours and was followed by a moderate decline. On the other hand, when prothrombin titration was carried out with the aid of the deprothrombinized sub-

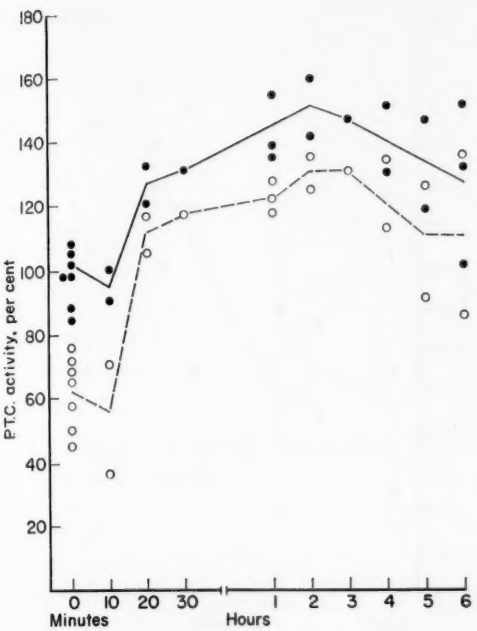


FIG. 2.

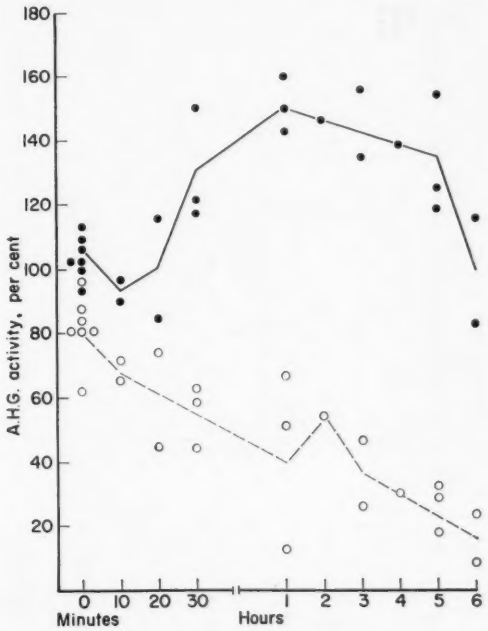


FIG. 3.

FIG. 2. Behavior of plasma thromboplastin component in isolated venous segments. The continuous line and the black circles represent determinations on untreated plasma. The broken line and the empty circles represent determinations on plasma incubated at 37 degrees C. for 16 hours. The increase in activity of plasma thromboplastin component within the segment is interpreted as expression of its activation to serum accelerator.

FIG. 3. Behavior of antihemophilic globulin in isolated venous segments. The continuous line and the black circles represent determinations on untreated plasma. The broken line and the empty circles represent determinations on plasma treated with barium sulfate. The latter values are true expressions of the concentration of antihemophilic globulin within the segment, whereas the former values represent the activity of some other more active intermediate product of the formation of thromboplastin.

strate described, a steady but very slow decrease was noted. After 6 hours, over 60 per cent of the prothrombin was still present within the segment (Table II).

The conversion of prothrombin to thrombin (Fig. 6). When barium sulfate-treated plasma from the occluded segments was incubated with prothrombin, thromboplastin, and calcium ions (Ca^{++}), the amount of thrombin evolved from the incubation mixture became progressively lower. After 6 hours, the thrombin formed did not exceed that obtained when isotonic saline was added to the incubation mixture instead of plasma. Since the only factor present in barium sulfate-treated plasma which acts on the conversion of prothrombin is labile factor, these results indicate a progressive depletion of this factor within the segment. Similar results were obtained when labile factor was determined in barium sulfate-treated plasma by the method of Wolf, but, when this determination was repeated in native plasma, it showed an increase in labile factor activity. When serum was added to the mixture of prothrombin, thromboplastin, and Ca^{++}, a progressive and steady increase in the amount of thrombin generated was noted (Fig. 6), but again this effect was abolished after treating the serum with barium sulfate.

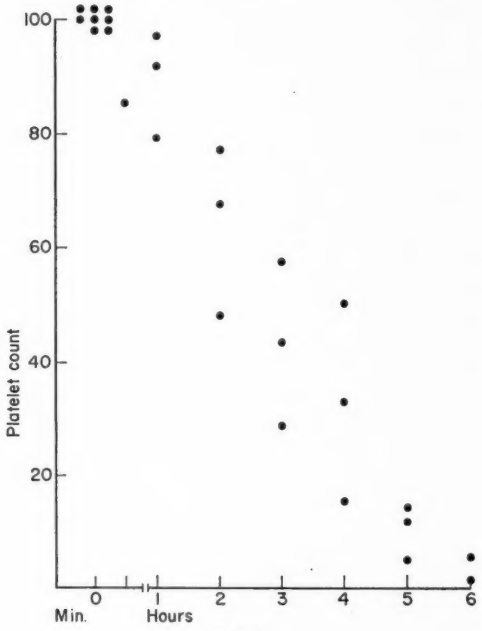


FIG. 4.

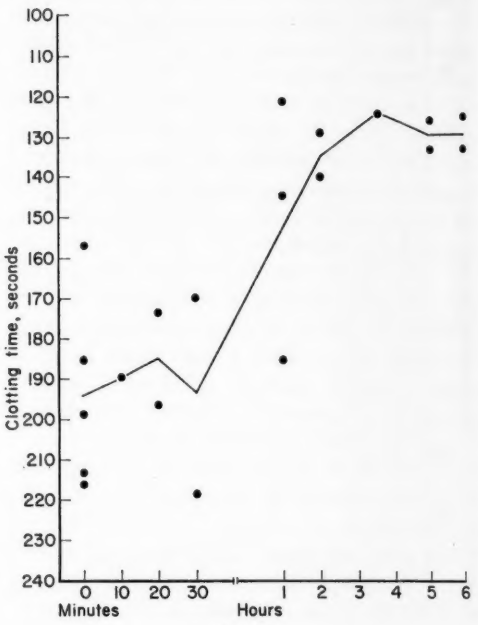


FIG. 5.

FIG. 4. Behavior of platelets in isolated venous segments. For purpose of clarity, each platelet count is expressed as a percentage of the total number of platelets in the general circulation.

FIG. 5. Behavior of platelet factor 3 in isolated venous segments. A shortening of the clotting time is indicative of increased activity.

Several factors present in the fraction absorbed by barium sulfate and able to accelerate the conversion of prothrombin in the presence of tissue thromboplastin have been described, such as proconvertin, autoprothrombin, and serum prothrombin conversion accelerator. The consensus is that these factors are closely related and may represent different physiologic aspects of the same substance, which is generally referred to as factor 7 or stable factor. Seegers and coworkers (14, 15) have provided suggestive evidence indicating that this substance may be a prothrombin derivative. Using purified substrates they were able to obtain this derivative from a mixture of prothrombin, labile factor, platelet factor 3, and Ca^{++}. In keeping with Seegers' view, one may then conclude that labile factor reacts within the segments with prothrombin and platelet factor 3 to form a new accelerator, probably identical with factor 7. This accelerator exhibits labile factor-like activity, but is removed from plasma and serum with the fraction absorbed by barium sulfate.

The generation of thrombin. Thrombin generation did not show changes for at least a half hour. During the second hour a marked increase in the generation of thrombin was noted. This was followed by a progressive and steady decline. Between the fourth and sixth hours, the thrombin generation was extremely poor (Table III).

Fibrinogen. Fibrinogen concentration varied very little. After 6 hours, over 70 per cent of the fibrinogen was still present within the segments (Table II).

Anticoagulants. Antithromboplastin did not change to any great extent. On the other hand, antithrombin underwent a sharp increment, reaching the climax in ½ hour. Antithrombin then declined and reached the

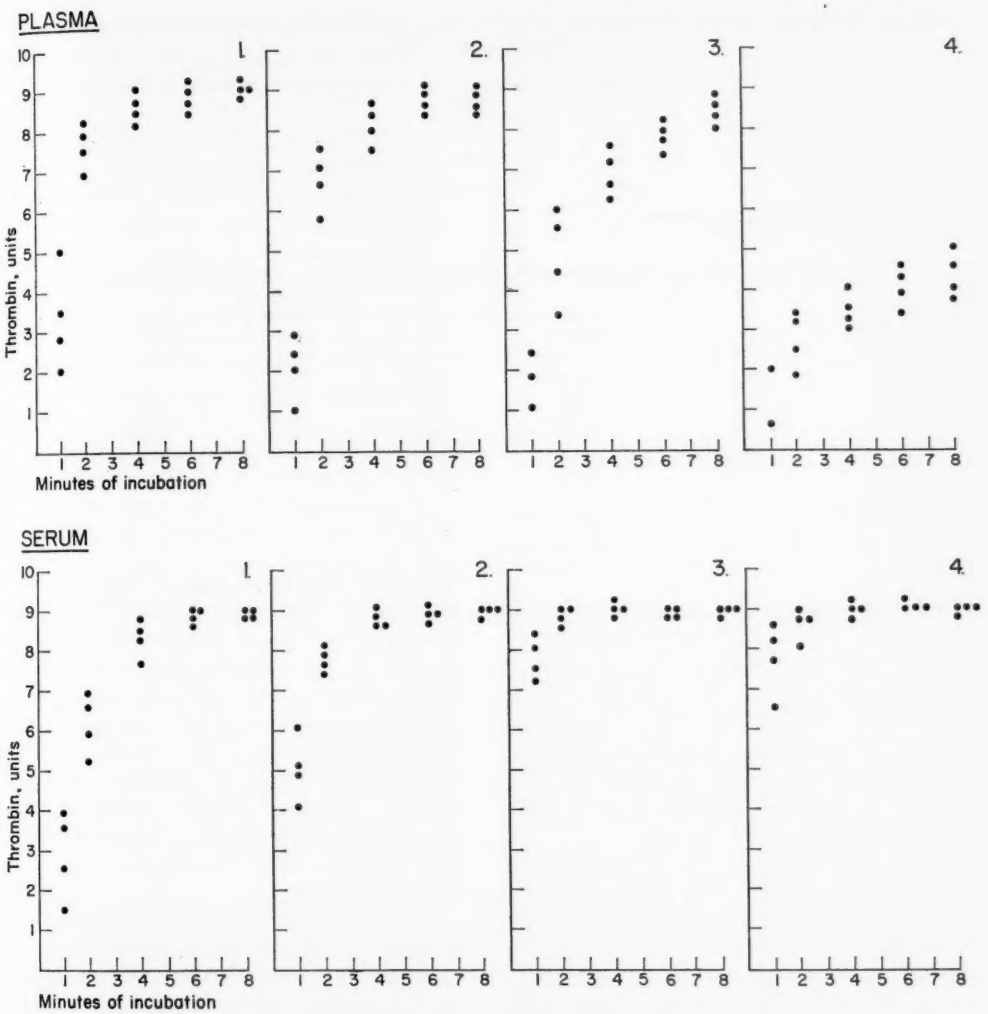


FIG. 6. Effects of the addition of barium sulfate-treated plasma or native serum on the evolution of thrombin from a mixture of prothrombin, thromboplastin, and Ca^{++}: (*1*) blood from the general circulation; blood from the segments: (*2*) 30 minutes after the interruption of blood flow, (*3*) 2 hours later, and (*4*) 6 hours later. Note the steady and progressive decrease in the amount of thrombin generated when barium sulfate plasma is added to the incubation mixture and the reciprocal behavior of thrombin generation when native serum is used.

base line between the second and third hours (Fig. 7).

The fibrinolytic system. Fibrinolysin or plasmin activity showed a pronounced decrease in the occluded segments during the first 2 hours of the experiment. After the second hour, fibrinolysin showed no change or, at best, a slight increment (Fig. 8). The activator of fibrinolysin underwent a sharp diminution in activity during the first half hour but then began to climb and ultimately reached a level higher than the original one (Fig. 9). The activity of the inhibitor of fibrinolysin remained sustained throughout.

TABLE II.—BEHAVIOR OF PROTHROMBIN ACTIVITY AND FIBRINOGEN CONCENTRATION IN ISOLATED VENOUS SEGMENTS

	General circulation	*Isolated segments — Times after interruption of blood flow*				
		30 mins.	*1 hr.*	*2 hrs.*	*4 hrs.*	*6 hrs.*
Prothr. time, secs. (Quick*)...	18.4	12.7	14.4	21.6	24.2	36.5
Prothr. activity, per cent.....	100	99.6	98.3	84.5	79.7	65.5
Fibrinogen, per cent.....	100	98.2	94.5	82.5	78.1	73.2

All data represent averages of 4 determinations.
*Plasma diluted 1:10 in veronal buffer.

TABLE III.—THE GENERATION OF THROMBIN IN ISOLATED VENOUS SEGMENTS

Incubation time of the generation mixture, mins.	*General circulation*	*Occluded segments — Times after occlusion of segment*				
		30 mins.	*1 hr.*	*2 hrs.*	*4 hrs.*	*6 hrs.*
		Seconds				
1	195.4	181.5	52.4	104.6	—	—
2	51.2	48.1	25.3	92.4	406.2	—
3	25.6	19.3	41.6	81.6	206.5	504.5
4	34.1	42.1	55.9	73.4	104.2	321.2
5	42.7	54.6	94.6	104.5	—	—
6	96.1	109.1	205.1	209.6	—	—

All data are averages of 3 determinations.

DISCUSSION

The significance of the results presented in this article can be fully appreciated in the light of previous reports on the coagulation of the blood in vitro. The initiation of the coagulation process and the intermediate steps in the generation of thromboplastin in vitro have been described by Margolis, Ratnoff and Rosenblum, Bergsagel (3, 4), Biggs and associates (6) and Hougie.

These reactions can be summarized as follows. Upon contact with glass, Hageman factor is activated and reacts with plasma thromboplastin antecedent to form a clot-promoting substance-contact factor or activation product. This in turn activates plasma thromboplastin component leading to the elaboration of a new coagulant agent which is not consumed during the coagulation of the blood and can thus be recovered in serum. This "serum accelerator" is responsible for the activity of serum in the thromboplastin generation test of Biggs and Douglas (5).

When serum is incubated with antihemophilic globulin, the mixture yields "product 1." This term is actually a misnomer, because this is not the first substance formed, but for convenience it will be used in this discussion. Product 1 induces in platelets the changes of "viscous metamorphosis." These consist of swelling of the platelet body, formation of pseudopods with fusion of adjacent platelets and rearrangement of the granules which are usually fairly well distributed within the platelet body to the periphery. Ultimately the platelets are lysed, thereby releasing platelet factor 3. This reacts with labile factor, product 1, Ca^{++}, and Stewart factor to produce "intrinsic thromboplastin."

Thromboplastin reacts with prothrombin to form a small amount of thrombin which, as a rule, is not sufficient to convert fibrinogen to fibrin. Thrombin, however, contributes to the activation of plasma thromboplastin component to "serum accelerator," according to Seegers (14) and Shanberge and associates, and to the lysis of platelets. In addition, thrombin transforms labile factor to serum labile factor, accelerin, a substance which accelerates the prothrombin conversion. As a result of this autocatalytic process, thrombin evolves with ever increasing speed from the mixture and ultimately reaches a concentration sufficient to cause the conversion of fibrinogen to fibrin, as stated by Quick (11).

It is generally assumed that the reactions leading to the coagulation of the blood in vitro, as described, cannot take place in vivo.

According to the classic theory regarding the genesis of intravascular thrombosis, this would follow the release into the circulation of tissue substances with thromboplastic activity. This "extrinsic thromboplastin," upon reaching the blood stream, combines with factor 7 and prothrombin to form a small amount of thrombin and thereby initiates the autocatalytic reaction. This mechanism, of course, requires the presence of tissue injury.

The present study indicates that intrinsic thromboplastin can form in vivo as well as in vitro, at least in areas of the vascular system containing stagnant blood. By interpolating the results obtained herein with the pattern of the coagulation in vitro as previously outlined, the sequence of events taking place in isolated venous segments can be reconstructed as follows: Within minutes from the interruption of blood flow, a clot-promoting substance similar to contact factor develops through the interreaction of Hageman factor and plasma thromboplastin antecedent. This substance activates plasma thromboplastin component to serum accelerator (Fig. 10, *1*).

Serum accelerator combines with antihemophilic globulin and Ca^{++} to form product 1. This in turn initiates the lysis of platelets, leading to the gradual release of platelet factor 3 (Fig. 10, *2*). This sequence, which takes place within minutes in vitro, takes up most of the first hour in occluded venous segments. At this point, nevertheless, all the factors indispensable for the formation of intrinsic thromboplastin are present within the segment.

Thus platelet factor 3, product 1, labile factor, and Ca^{++} react with prothrombin to form a small amount of thrombin. At this time, some fibrin formation may occur within the segments. The amount of thrombin thus processed, however, is not sufficient to cause the immediate and massive coagulation of the blood. In addition, thrombin is immediately inactivated by antithrombin (Fig. 10, *3*). The origin of this antithrombin is still a matter of speculation. Mucopolysaccharides with heparin-like activity have been described in the wall of the vessels, especially of the arteries. Heparin is also the anticoagulant principle contained in the mast cells, which are particularly abundant in the wall of the veins. Antithrombin is also possibly elaborated within the circulating blood itself. Thus, serum contains a protein capable of inactivating thrombin which, by electrophoretic separation, migrates according to Quick (12), with the alpha globulin fraction. Our study does not provide a satisfactory explanation for the mechanism of formation of antithrombin, but it re-emphasizes its role in preserving the fluidity of the blood in vivo. An important effect of the prompt neutralization of thrombin is that the autocatalytic reaction cannot gain momentum.

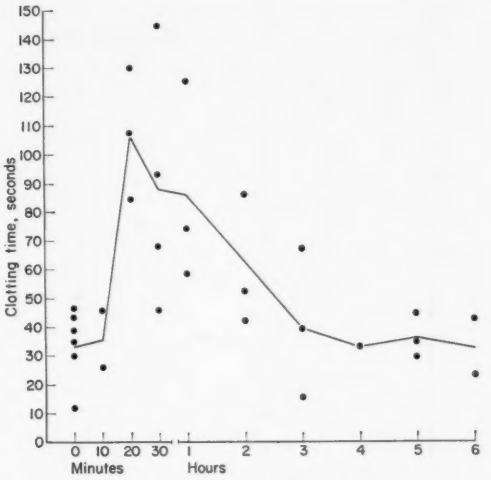


FIG. 7. Behavior of antithrombin in isolated venous segments. Data were obtained by incubating serum and thrombin for 10 minutes.

While the conversion of prothrombin to thrombin comes to a standstill, another prothrombin derivative is elaborated within the segments. This substance is ineffective in the coagulation of fibrinogen but has the prop-

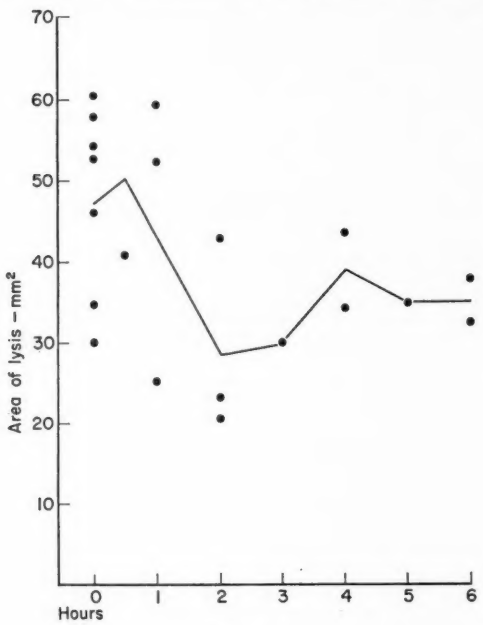


FIG. 8.

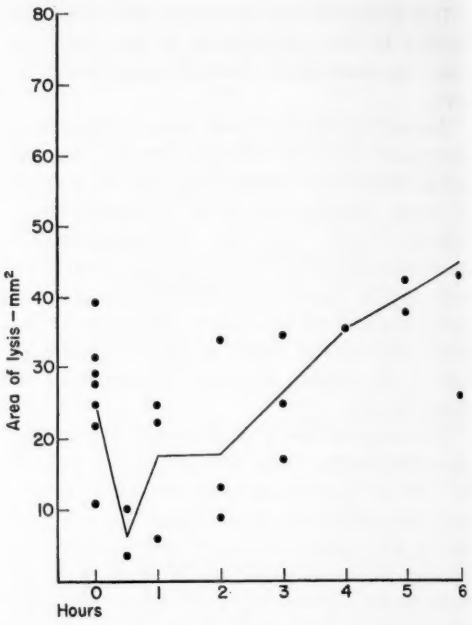


FIG. 9.

FIG. 8. Behavior of fibrinolysin in isolated venous segments.
FIG. 9. Behavior of the activator of fibrinolysin in isolated venous segments.

erty of enhancing the conversion of prothrombin in the presence of tissue thromboplastin. This serum prothrombin conversion accelerator, factor 7, forms in blood when prothrombin reacts with platelet factor 3, labile factor, and Ca^{++} (Fig. 10, *4*). Prolonged stagnation, by causing an increase in platelet factor 3 concentration, may lead also to the elaboration of large quantities of this accelerator, especially when the normal pathway of thrombin formation is impaired. Since this accelerator requires tissue thromboplastin to exert its effect, its presence in the circulation is of no consequence on the overall coagulability of the blood as long as the integrity of the vascular endothelium is preserved. On the other hand, when a vessel is sectioned, this accelerator increases the effectiveness of tissue thromboplastin released at the site of injury, thus assuring prompt hemostasis.

Antihemophilic globulin and labile factor are slowly consumed within the segments and disappear almost entirely in 6 hours, but their activity is not completely dissipated. Antihemophilic globulin, in fact, contributes to the release of platelet factor 3, which, in turn, reacts with labile factor, prothrombin, and Ca^{++} to form "serum prothrombin conversion accelerator." As a result of these reactions, the "intrinsic coagulation" of the blood is impaired because of the exhaustion of antihemophilic globulin and labile factor, but the hemostatic process retains its ability to function much longer since this is largely dependent upon the release of extrinsic thromboplastin at the site of the injured vessel.

From the present study, the role of the fibrinolytic system in the preservation of the fluidity of the blood appears ambiguous. In fact, at no time was an increase of fibrinolytic activity noted within the segments. This phenomenon is related possibly to the fact

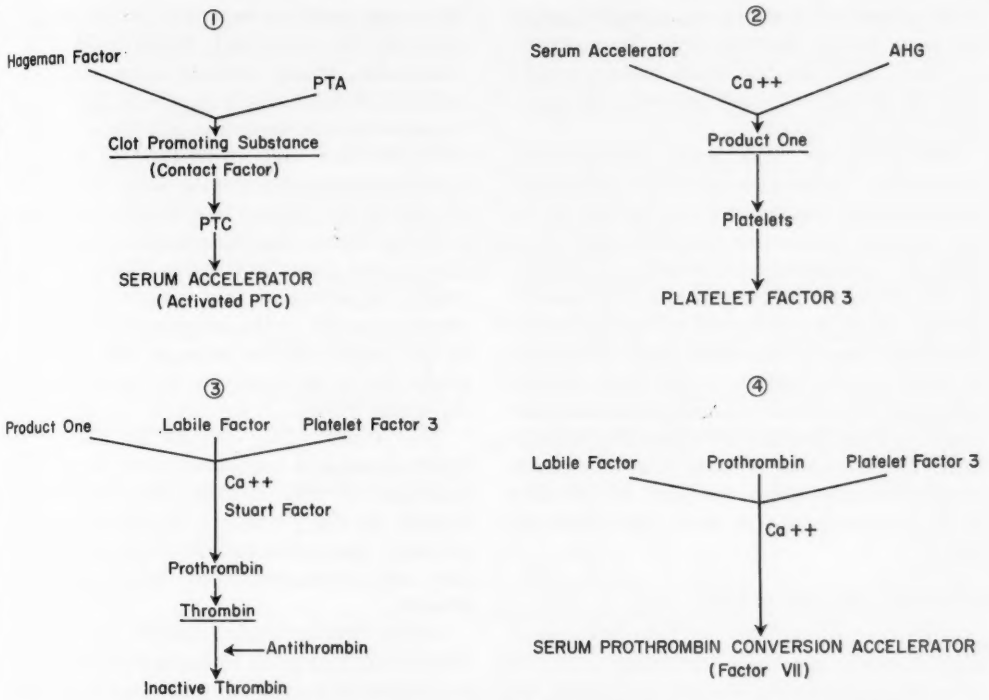


FIG. 10. Summary of the coagulation of blood in isolated venous segments: The coagulation process exhausts itself without achieving the formation of a solid clot because of slow thrombin formation and its rapid inactivation by antithrombin. Platelets are lysed, releasing their thromboplastic factors. Two accelerators are elaborated—serum accelerator, a product of the activation of plasma thrombin component, and serum prothrombin conversion accelerator, factor 7, a product of the activation of prothrombin.

that the level of antifibrinolysin in blood is 20 to 30 times greater than that of fibrinolysin. It is also conceivable that fibrinolysin may be adsorbed on the small fibrin clots which form within the segments, a fact which could account for the poor consistency of the clots. Should normal circulation be restored, these clots would almost certainly be swept away and lysed without giving rise to serious embolization.

The application of these findings to human pathology allows some interesting observations in regard to the role of stasis in the pathogenesis of intravascular thrombosis. It is well known that homologous serum, administered intravenously to an animal, can lead to intravascular thrombosis in areas of stasis. The active substance in serum derives from the activation of plasma thromboplastin component by contact factor. It has hitherto been assumed that this activation can take place only when blood is exposed to a foreign surface. This concept finds confirmation in the fact that blood can be made to clot immediately within a vessel if it is aspirated into a glass syringe and reinjected a few minutes later. Findings in the present study would imply that the factor responsible for the activity of serum can be elaborated within the vascular system itself in the presence of prolonged stagnation. Although the protective mechanism just described would not ordinarily allow the formation of a thrombus, it is conceivable that in patients suffering from congestive heart failure or confined to bed,

large amounts of serum accelerator might be continuously elaborated in the most dependent parts of the body which would make these patients more prone to thromboembolic phenomena.

On the other hand, serum prothrombin conversion accelerator, factor 7, may play an important role in the mechanism of intravascular thrombosis in the surgical patient and in the pregnant woman at the time of delivery. Blood stasis is a common feature in both of these conditions and may lead to the production of unusually great quantities of serum prothrombin conversion accelerator. This in turn could trigger the mechanism of intravascular thrombosis by potentiating the effects of minute amounts of extrinsic thromboplastin released in the area of the surgical wound or at the placental site.

SUMMARY AND CONCLUSIONS

Segments of jugular veins were isolated in dogs between 2 totally occluding vascular clamps. Coagulation studies conducted on blood obtained from the segments at different intervals of time for 6 hours provide a dynamic picture of the coagulation process within the segments. This process can be divided into three phases. The first phase lasts about 1 hour. The dominant event during this phase is the sequence leading to the lysis of platelets. This sequence initiates with the activation of Hageman factor and plasma thromboplastin antecedent to a "clot promoting substance" which, in turn, activates plasmin thromboplastin component to serum accelerator. Serum accelerator then reacts or combines with antihemophilic globulin to form product 1, the agent responsible for the lysis of platelets. Near the end of the first hour, platelet factor 3 appears in large quantity in the segments and reacts with plasma thromboplastin factors to form intrinsic thromboplastin.

The second phase lasts about 2 hours. During this phase some thrombin is generated in the segments, but not in sufficient quantity to maintain sustained activation of the autocatalytic reaction. In addition, thrombin is immediately inactivated by antithrombin. Small clots may form within the segments but these are very soft and friable because of poor thrombin activity and, possibly, the fact that fibrinolysin is incorporated in the substance of the clots. The return of normal circulation would almost certainly bring about the disintegration of these clots before they could cause serious embolization. However, should these clots form in areas favorable to the lodging of a clot, such as the valves of the veins of the leg, they could very well constitute the starting point for a thrombus.

The third phase begins at about the fourth hour and is characterized by the exhaustion of the clotting process. This is caused by the depletion of antihemophilic globulin and labile factor, while prothrombin and fibrinogen show only moderate change.

While the intrinsic coagulation of the blood exhausts itself without achieving the formation of a solid clot, another coagulant agent is elaborated within the segments. This agent accelerates the conversion of prothrombin to thrombin in the presence of tissue thromboplastin and is thus related to factor 7. This accelerator probably derives from the interreaction of prothrombin, platelet factor 3, labile factor, and Ca^{++}. It has no effect on the intrinsic coagulation of the blood but is important in hemostasis.

The results presented in this article imply that clot promoting agents, effective in either the intrinsic or extrinsic coagulation of the blood, may be elaborated in areas of the vascular system containing stagnant blood. These accelerators may play a role in the genesis of thromboembolism in patients in congestive failure, in the surgical patient, and in the pregnant woman at the time of delivery.

REFERENCES

1. Adams, D. M. Rapid method for determination of plasma fibrinogen. Proc. Soc. Exp. Biol., N. Y., 1960, 103: 107.
2. Bell, W. N., and Alton, H. G. A brain extract as a

substitute for platelet suspensions in the thromboplastin generation test. Nature, 1954, 174: 880.
3. BERGSAGEL, D. E. Viscous metamorphosis of platelets; morphological platelet changes induced by an intermediate product of blood thromboplastin formation. Brit. J. Haemat., 1956, 2: 130.
4. BERGSAGEL, D. E., and HOUGIE, C. Intermediate stages in the formation of blood thromboplastin. Brit. J. Haemat., 1956, 2: 113.
5. BIGGS, R., and DOUGLAS, A. S. The thromboplastin generation test. J. Clin. Path., Lond., 1953, 6: 23.
6. BIGGS, R., DOUGLAS, A. S., and MACFARLANE, R. G. The formation of thromboplastin in human blood. J. Physiol., Lond., 1953, 119: 89.
7. HOUGIE, C. The role of factor V in the formation of blood thromboplastin. J. Laborat. Clin. M., 1957, 50: 61.
8. MARGOLIS, J. Initiation of blood; coagulation by glass and related surfaces. J. Physiol., Lond., 1957, 137: 95.
9. MARIN, H. M., STEFANINI, M., HEIKINHEIMO, R., and SOARDI, F. Coagulation changes in experimental phlebothrombosis. Surg. Gyn. Obst., 1960, 110: 541.
10. PITNEY, W. R., and DACIE, J. V. A simple method of studying the generation of thrombin in recalcified plasma. Application in the investigation of haemophilia. J. Clin. Path., Lond., 1953, 6: 9.
11. QUICK, A. J. On the probable mechanism of intravascular clotting. Angiology, 1956, 7: 419.
12. Idem. The physiologic protective mechanism against intravascular clotting. Angiology, 1959, 10: 386.
13. RATNOFF, O. D., and ROSENBLUM, J. M. Role of Hageman factor in the initiation of clotting by glass; evidence that glass frees Hageman factor from inhibition. Am. J. Med., 1958, 25: 160.
14. SEEGERS, W. H. The activation of prothrombin. Angiology, 1956, 7: 436.
15. SEEGERS, W. H., ALKJAERSIG, N., and JOHNSON, S. A. Formation of autoprothrombin in solutions containing purified prothrombin and purified platelet factor 3. Am. J. Physiol., 1955, 181: 589.
16. SHANBERGE, J. N., SARELIS, A., and REGAN, E. E. The effect of heparin on plasma thromboplastin formation. J. Laborat. Clin. M., 1959, 54: 501.
17. SOARDI, F. G., STEFANINI, M., STUMP, D. J., and MARIN, H. M. The components of the fibrinolytic system in a venous segment undergoing experimental thrombosis. Surg. Gyn. Obst., 1960, 111: 135.
18. STEFANINI, M., and DAMESHEK, W. The Hemorrhagic Disorders; a Clinical and Therapeutic Approach. New York: Grune & Stratton, Inc., 1955.

EXPERIMENTAL STUDIES AND CLINICAL EXPERIENCE WITH ISOLATED LIMB PERFUSION OF FUNGICIDAL DRUGS

ERIC W. FONKALSRUD, M.D., JOYCE SHINER, B.S., ROBERT HAAN, M.D., SAMUEL A. MARABLE, M.D., VICTOR NEWCOMER, M.D., and DONALD B. ROCHLIN, M.D., Los Angeles, California

SUCCESSFUL TREATMENT of deep mycotic infections has been accomplished by prolonged intravenous administration of amphotericin B. Most favorable results have been obtained in mild acute fungus infections with less gratifying responses in similarly treated advanced chronic lesions. The systemic toxic results after administration of amphotericin B frequently limit its effectiveness in the treatment of chronic mycotic infections of the extremities and other localized areas as indicated in the reports of Beard and Halde and their associates.

The isolated limb perfusion technique, described by Creech and his co-workers for the treatment of peripheral neoplasms provides a method of delivering a high drug concentration to localized areas while minimizing the toxic effects of the agent used. Experimental and clinical evaluations of the toxicity and effectiveness of amphotericin B when administered by the isolated limb perfusion technique are reported herein.

EXPERIMENTAL STUDIES

Toxicity studies were carried out on adult mongrel dogs after intravenous infusion of amphotericin B and a minimum lethal dose was determined. After the drug was dissolved in 500 milliliters of 5 per cent dextrose and water, it was given intravenously to lightly anesthetized dogs. Blood urea nitrogen, creatinine, thymol turbidity, and total bilirubin determinations were obtained as controls and were made on the 5 successive days subsequent to infusion. A marked rise in the blood urea nitrogen and creatinine levels was noted on the first and second days after infusion with a rapid return to normal within 3 days in the survivors (Fig. 1). The changes in thymol turbidity and total bilirubin were negligible in all the animals. The minimum lethal dose of amphotericin B was 7.0 milligrams per kilogram of body weight in this series. Isolated hind limb perfusion was performed on 5 adult mongrel dogs utilizing the Sigmamotor pump and a disposable bubble oxygenator (Fig. 2). These animals were anesthetized with pentobarbital sodium, and after exposure of the common femoral vessels, 2.0 milligrams per kilogram of body weight of heparin were given. After cannulation of the vessels, a tourniquet placed proximally was tightened to occlude venous flow. Perfusion was then carried out matching the arterial flow with the venous return. In 2 animals, 3 milligrams and, in 3 animals, 6 milligrams of amphotericin B per kilogram of body weight were dissolved in 100 milliliters of dextrose and water and added to the arterial reservoir. Warmed heparinized whole blood was used as the perfusate. After a 30 minute perfusion period, the circuit was drained and washed with 300 milliliters of fresh blood. No deaths occurred in the series, but there was moderate, transient limb edema in each animal. There was a more severe swelling, however, and an inability to ambulate upon the perfused limb in 2 of the animals given the greater doses.

In an attempt to reduce edema and con-

From the Departments of Surgery and Dermatology, University of California Medical Center, Los Angeles.

This investigation was supported by the U. S. Public Health Service Grant-in-Aid No. CYP-5049 and The Blalock Foundation.

gestion of the extremity after perfusion, a simplified technique of needle cannulation and syringe perfusion was performed in another series of 5 dogs. The animals were anesthetized and heparinized as in the previous group, and a No. 18 gauge needle was inserted distally into the exposed femoral artery. A No. 15 gauge needle was placed into the vein. Both needles were secured by means of ligatures about the vessels which were then clamped proximally, and the tourniquet was tightened. Three hundred milliliters of oxygenated, heparinized blood with 8 milligrams of amphotericin B per kilogram of body weight, dissolved in 100 milliliters of dextrose and water, were used as the perfusate and infused into the artery by syringe. Arterial flow was matched accurately with venous return which was collected in a calibrated reservoir. The circuit was washed with 250 milliliters of heparinized blood upon completion of perfusion. In 2 instances, 5 per cent dextrose and water without blood was used as the perfusate. Moderate swelling of the limb occurred postoperatively in the latter 2 cases. Blood was used as the perfusate in 3 instances, and there was negligible swelling and the animals were able to ambulate on the perfused limb the day after operation. Radioactive chromium tagged red cells were added to the perfusate in 2 instances, and the average spillover into the systemic circulation after 30 minutes of perfusion was 15 per cent. Samples were obtained from the forepaw at 10 minute intervals, and the maximum spillover occurred after the 30 minutes of perfusion. During the 5 days after operation none of the blood urea nitrogen or creatinine levels exceeded 42.6 milligrams per cent or 1.33 milligrams per cent, respectively (Table I).

A method of taking advantage of simple needle perfusion in a larger extremity as well as providing maximum oxygenation for optimum drug absorption was devised (Fig. 3). Five dogs were anesthetized, heparinized, and isolated as in the previous series, and a No. 21 gauge needle was inserted into the

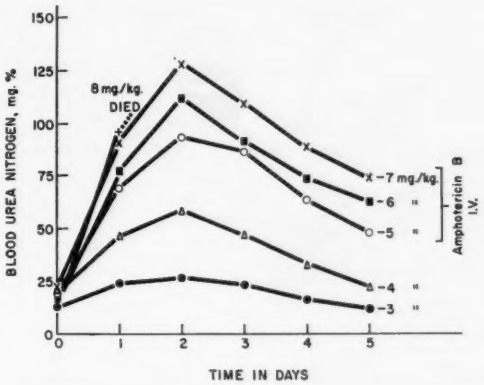


FIG. 1. Toxicity changes in blood urea nitrogen on successive days after intravenous administration of amphotericin B solution. Each line represents average of 3 animals.

femoral artery. The corresponding femoral vein was cannulated with a No. 15 gauge needle and the blood was allowed to drain by gravity into a calibrated reservoir. The artery was partially occluded immediately proximal to the needle by means of a calibrated, partial occlusion clamp. Flow in the artery was reduced to approximately one-third of normal by narrowing the external diameter of the vessel from 60 to 70 per cent of its normal size. Eight milligrams of amphotericin B per kilogram of body weight were dissolved in 50 milliliters of 5 per cent dextrose and water and infused slowly by syringe distally into the femoral artery. Upon completion of infusion, the circuit was washed with 250 milliliters of fresh

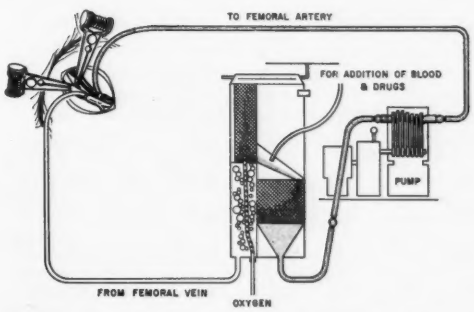


FIG. 2. Isolated limb perfusion technique using disposable bubble oxygenator and Sigmamotor pump.

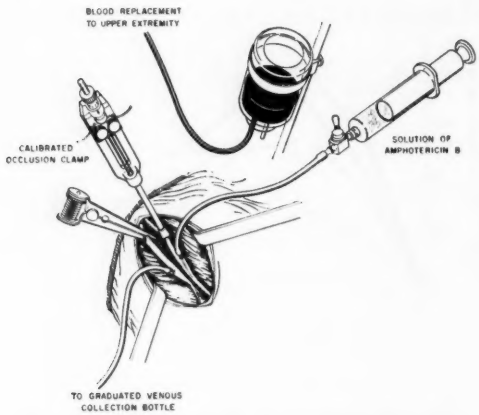

BLOOD REPLACEMENT TO UPPER EXTREMITY
CALIBRATED OCCLUSION CLAMP
SOLUTION OF AMPHOTERICIN B
TO GRADUATED VENOUS COLLECTION BOTTLE

FIG. 3. Diagram of simplified isolated limb infusion technique with needle cannulation, partial arterial occlusion, syringe infusion, and systemic blood replacement.

blood. Simultaneously with the perfusion, an equal volume of heparinized blood was administered intravenously through a forepaw to match the blood obtained from the femoral vein. The limb swelling was negligible, and each animal was able to ambulate on the perfused leg on the first postoperative day (Table II). The blood urea nitrogen and creatinine levels remained low in each case (Figs. 4 and 5).

In 3 instances, the needle cannulation and partial arterial occlusion techniques were used in conjunction with perfusion of the upper lobe of the right lung. By right thoracotomy, the pulmonary artery and vein to the upper lobe of the right lung were cannulated with needles and perfused in a manner similar to that already described. The artery was partially occluded proximal to the site of the needle puncture and 100 milliliters of amphotericin B solution were infused into the vessel by syringe. The dose of amphotericin B was lowered to 2 milligrams per kilogram of body weight in these cases. One animal died 7 days postoperatively as a result of empyema of the right pleural cavity, but the other 2 animals were long term survivors and showed no evidence of atelectasis of the upper lobe of right lung.

TABLE I.—LIMB ISOLATION WITH NEEDLE CANNULATION AND SYRINGE PERFUSION

Animal	*Perfusate*	*Dose amphotericin B (mgm./kgm.)*	*Total dose amphotericin B, mgm.*	*Maximum value (mgm. per cent) BUN*	*Creatinine*	*Postoperative course*
NP1	Whole blood	8	136	35.4	0.97	Minimal swelling
NP2	Whole blood	8	132	42.6	0.86	Minimal swelling
NP3	Whole blood	8	120	36.5	1.02	Mild swelling
NP4	D5W	8	135	37.9	1.33	Moderate swelling
NP5	D5W	8	129	33.5	0.93	Marked swelling withskin ulceration

CLINICAL EXPERIENCE

Three patients with peripheral coccidioidomycosis and 1 patient with maduromycosis of the foot were treated by isolated limb perfusion with amphotericin B. In each case, prolonged intravenous administration was unsuccessful. In 3 patients the pump oxygenator technique was used while in the fourth patient the needle cannulation and syringe perfusion technique was used. One patient with cutaneous coccidioidomycosis has experienced a clinical remission of 17 months. Transient remissions occurred in 2 other patients with more severe peripheral coccidioidomycosis with osteomyelitis and abscess formation.

REPORTS OF PATIENTS

PATIENT 1. A 54 year old Negro male plasterer was infected with Coccidioides immitis 8 years prior to admission when a severe respiratory infection developed as well as draining cutaneous nodules of the nose. Several hyperkeratotic and hyperpigmented lesions, 0.5 to 1.0 centimeter in diameter, gradually appeared on the palmar surface of the left hand (Fig. 6). The nasal lesions and the pulmonary infection cleared after prolonged administration of amphotericin B and careful supportive management, but the nodules on the hand showed no improvement. Microscopic sections from multiple biopsies of the palmar lesions demonstrated typical coccidioidal spherules. Progressive edema of the left hand with associated discomfort and loss of function caused difficulty in his maintaining employment.

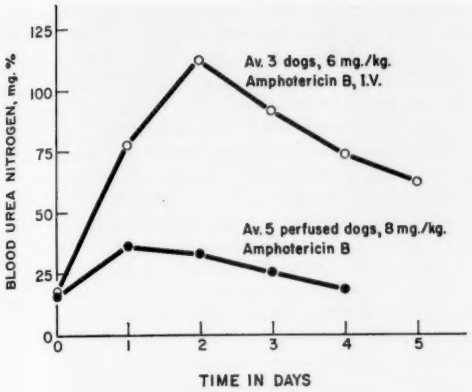


FIG. 4.

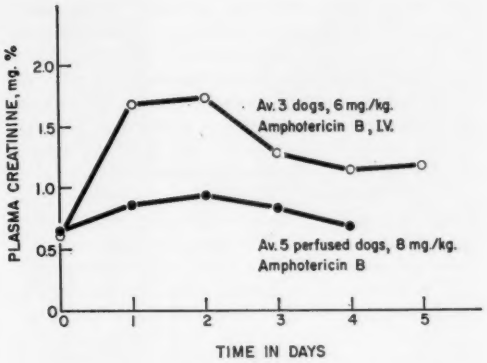


FIG. 5.

FIG. 4. Graph comparing changes in blood urea nitrogen on successive days after intravenous administration of amphotericin B solution and isolated limb perfusion using the syringe perfusion technique.

FIG. 5. Graph comparing changes in plasma creatinine on successive days after intravenous administration of amphotericin B solution and isolated limb perfusion.

When hospitalized, his complement fixation titer for coccidioidomycosis was recorded at 1:128. A 20 milligram dose of amphotericin B was administered intravenously 3 times weekly, and the patient was placed at rest. Small transient and rapidly reversible elevations in the blood urea nitrogen occurred during treatment. After 1 month of therapy there was no apparent change in the clinical appearance of the lesions of the hand, and isolation perfusion of the left arm was carried out. Under general anesthesia and with the patient's left arm isolated by means of a pneumatic cuff, the brachial artery and vein were cannulated above the elbow. Using the Sigmamotor pump and disposable bag bubble oxygenator, the extremity was perfused with heparinized blood and 30 milligrams of amphotericin B. After 1 hour of perfusion, the arterial circuit was flushed with fresh blood and the vessels were reconstituted.

Postoperatively, there was a slight increase in the edema of the arm with considerable erythema and hypersensitivity about the lesions of the left palm. A transient low grade fever developed but there was no elevation in the blood urea nitrogen level. The edema of the hand decreased and the cutaneous lesions subsided. Since discharge, the patient has been actively engaged as a plasterer and has had no notable discomfort or apparent disability. Several months after perfusion, a repeat biopsy of 1 of the remaining small lesions showed scarring without spherules. Culture from this biopsy specimen grew no organisms. One month after perfusion, a small amount of fluid was aspirated from the left wrist and it was found to contain Coccidioides immitis upon culture. Although the patient apparently continues to have a residual coccidioidal infection, as measured by a complement fixation titer of 1:256 approximately 1 year after perfusion, he has remained completely asymptomatic with a subsidence of the cutaneous lesions (Fig. 7).

PATIENT 2. A 39 year old male Negro developed pneumonitis, presumably coccidioidal, about 7 years before admission. Six months after the pulmonary infection, moderate injection and swelling of the right wrist and hand were noted. Later a draining osteomyelitis developed and cultures indicated Coccidioides immitis. Over a period of several years several drainage and saucerization procedures were performed, and an attempt was made to fuse the right wrist. Intravenous amphotericin B was given for a prolonged period as well as various other antifungal agents without notable improvement and, finally, amputation was advised. Isolation perfusion was recommended as a last resort however.

TABLE II.—LIMB ISOLATION, PARTIAL ARTERIAL OCCLUSION, NEEDLE CANNULATION, AND SYRINGE INFUSION

Animal	*Dose amphotericin B (mgm./kgm.)*	*Total dose amphotericin B, mgm.*	*Maximum value — (mgm. per cent)— BUN*	*Creatinine*	*Postoperative course*
PO1	8	104	40.2	1.12	Minimal swelling
PO2	8	200	29.3	0.86	No swelling
PO3	8	112	35.2	0.91	Negligible swelling
PO4	8	110	37.5	0.87	No swelling
PO5	8	140	39.5	0.99	Minimal swelling

Using the pump oxygenator system, the isolated right upper extremity was perfused for 1 hour. Heparinized blood and 50 milligrams of amphotericin B solution were used as the perfusate. The circuit was flushed with fresh heparinized blood after perfusion. For several days postoperatively, there was considerable inflammation and edema about the draining area of the wrist associated with a mildly febrile course. The blood urea nitrogen level at no time after perfusion rose above 14 milligrams per cent and no change was noted in the complement fixation titer for coccidioidomycosis. The edema and inflammation about the wrist decreased with moderate improvement of the condition, but the draining osteomyelitis persisted and subsequent amputation was necessary.

PATIENT 3. Seven years prior to admission, a 54 year old white male first noticed a persistent lesion of the left heel after a puncture wound by a wood splinter. Subsequently, numerous draining sinuses developed, and the entire left foot became markedly swollen and indurated (Fig. 8). Cultures taken of the drainage revealed Monosporium apiospermum (madduromycosis). Deep x-ray therapy and streptomycin were prescribed but without apparent improvement. Amphotericin B was given intravenously but the therapy was discontinued because of severe renal toxicity, as evidenced by an abrupt rise in blood urea nitrogen and creatinine levels. A new antifungal preparation, primaricin, also failed. Because of marked discomfort, restriction of ambulation, and progression of the disease, isolation perfusion was recommended in an attempt to avoid amputation.

The isolated left lower extremity was perfused for 1 hour with a solution of heparinized blood and 75 milligrams of amphotericin B. After perfusion, the blood urea nitrogen level did not rise above 20 milligrams per cent. A transient increase in edema and erythema developed postoperatively in the foot but gradually subsided to preperfusion status.

PATIENT 4. A 64 year old white male electronics technician first had pulmonary tuberculosis in 1934. Bed rest was required intermittently during the ensuing years in various institutions. In 1948, a draining abscess of the right ankle developed from which acid fast bacilli were cultured. During the next year osteolytic changes occurred in both lower extremities with swelling and drainage from both heels. Cultures from curette biopsy specimens were positive for Coccidioides immitis, and microscopic sections revealed numerous spherules. Multiple blebs in both upper lobes developed as well as a recurrent left pleural effusion. The tuberculosis osteomyelitis progressed to the left femur and tibia despite long term chemotherapy. In 1950, arthrodesis and arthrotomy of the left knee were carried out. Tissue from this area and from the sinus on the left heel again grew Coccidioides immitis upon culture. Osteolytic lesions then developed in several ribs, the pelvis, skull, and lumbar spine which were considered coccidioidal in origin. Amputation above the left knee was necessary in 1952 because of progressive infection and marked pain. Mycostatin and amphotericin B were administered intermittently for years with gradual regression of most of the bone lesions. However, the patient developed toxic manifestations to both of the drugs and, accordingly, therapy was discontinued. The sinus of the right heel continued to drain intermittently during the ensuing years. The complement fixation titer for coccidioidomycosis was 1:64 in 1955. In November 1960, the patient fell and twisted his right ankle and subsequently drainage from the heel increased (Fig. 9a and b). Culture of the drainage was positive for pseudomonas, and a curette biopsy revealed many spherules. The complement fixation titer was 1:32 upon admission in December. Because of the persistent peripheral coccidioidal osteomyelitis and the patient's sensitivity to amphotericin B, isolation perfusion was advised.

After spinal anesthesia, the ankle and lower leg were heated with circulating water pads. After heparinization, a 22 gauge needle was inserted distally into the exposed femoral artery and a small polyethylene catheter was placed into the femoral vein and the vessel was clamped proximally. This catheter was extended off the operating table and into a graduated cylinder. The proximal pneumatic tourniquet was set at 120 millimeters of mercury. A 500 millimeter bottle of dextrose and water containing 200 milligrams of amphotericin B was connected to a large syringe with a 3 way stopcock on the operating table and the solution injected into the artery for 45 minutes. Additional blood was allowed to flow through the femoral artery at the conclusion of the perfusion to wash out the excess amphotericin solution that remained in the vessels. The venous return from the femoral vein measured 2,000 cubic centimeters at the conclusion of the procedure. Concomitantly, 4 units of blood were infused through the forearm. The arterial puncture was controlled by finger pressure alone, and the venotomy was closed with a small row of sutures.

Following perfusion, the draining sinus was debrided and the foot kept warm. Broad spectrum antibiotics and amphotericin B were placed in the sinus intermittently for several weeks. The drainage gradually decreased and the sinus slowly filled in with scar tissue; however, a repeat biopsy 6 weeks after perfusion revealed occasional Coccidioides immitis spherules. After discharge from the hospital the patient ambulated without discomfort and there has been minimal drainage (Fig. 10).

DISCUSSION

The effectiveness of amphotericin B in the treatment of chronic mycotic infections

FIG. 6.

FIG. 7.

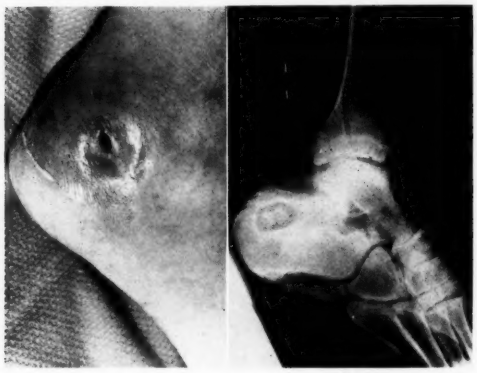
FIG. 6. Patient 1. Left hand prior to isolation perfusion. Note the cutaneous coccidioidal lesions and edema of the dorsal surface.

FIG. 7. Patient 1. Seventeen months after isolation perfusion with amphotericin B.

has been well documented in recent clinical reports. Favorable results were obtained when the drug was used in the treatment of coccidioidomycosis, cryptococcosis, North and South American blastomycosis, histoplasmosis, aspergillosis, sporotrichosis, and chromoblastomycosis. Intravenous administration seems to be the most satisfactory method at present. It is reasonably well established that amphotericin B is poorly absorbed from the gastrointestinal tract and that even prolonged large doses given by this route, in the majority of instances, fail to influence the clinical course of the systemic mycoses. Prolonged intravenous infusion is frequently accompanied by phlebitis at the site of infusion. Other reported manifestations of toxicity include: a rise in the blood urea nitrogen level with associated decreased glomerular filtration, decreased renal plasma flow, transitory vestibular disturbances, flushing, sweating, drowsiness, hypokalemia, and weight loss.

Because less favorable results have been obtained in the treatment of peripheral chronic deep mycotic infections than in the mild acute disseminated lesions, an attempt was made to provide much larger quantities of the drug to the involved extremity while minimizing systemic toxic manifestations. Isolated limb or organ perfusion may be utilized in cases which are refractory to long term parenteral administration of amphotericin B or in patients who manifest toxicity symptoms when the drug is given

FIG. 8. Patient 3. Left foot immediately prior to isolation perfusion. Note the multiple draining sinuses and marked edema of the dorsal surface of the foot.



a b

FIG. 9. Patient 4. a, Photograph and b, roentgenogram showing draining sinus with surrounding inflammatory reaction and osteolytic space in underlying calcaneus.

intravenously. Perfusion may be accompanied by intravenous infusion, both preoperatively and postoperatively, to maintain a prolonged circulating blood level of the drug. The accompanying parenteral infusion may best be monitored by frequent blood urea nitrogen determinations and clinical evidence of toxicity, as mentioned.

Perfusion of chemotherapeutic agents using the pump oxygenator has occasionally been accompanied by thrombophlebitis, edema, congestion, and peripheral neuritis in clinical experiences. Vesicant agents circulated through a vascular bed under high pressure cause increased fragility of the fine vascular channels resulting in much of the edema and congestion observed after isolated pump perfusion procedures. The importance of maintaining high arterial pressures in the perfused bed to obtain maximum drug absorption has not been well established. The maintenance of a high oxygen saturation in the perfusate for optimal tissue drug absorption has been advocated by Ryan and associates. Partial arterial occlusion with simple needle cannulation immediately distal to the tourniquet provides oxygenated blood quite readily in a well ventilated patient. Recent experimental work by Hottinger and associates indicates that oxygen consumption by the perfused extremity does not vary significantly with flow rates but is proportional to temperature changes in the isolated limb. From these data and the experimental work of Shingleton and Parker it may be inferred that maximum drug absorption occurs under hyperthermic conditions.

The experimental data from the present studies indicate that simple rubber tourniquet isolation of the dog's hind limb lowers the arterial blood flow in the distal femoral artery by approximately 25 per cent, as determined by a gated sine wave electromagnetic flowmeter. The partial occlusion clamp was employed simply to decrease further the arterial flow. The data compiled by Mann and associates indicate that a decrease in external arterial diameter of approximately 65 per cent will decrease the vascular flow by 70 per cent. Technically, a pneumatic tourniquet may be used more easily in human beings than in the dog. Partial inflation of the cuff to 100 to 200 millimeters of mercury, depending on the size of the extremity, will decrease arterial flow to a similar range and obviate the necessity of a partial occlusion clamp. A proportionate decrease in arterial pressure is associated with the decreased flow. The decreased flow permits longer perfusion with less systemic blood replacement. With lower arterial flow there is an associated decreased venous return and, accordingly, a large needle may be used for cannulation precluding the customary arteriotomy and venotomy incisions. The lower arterial pressure is probably a significant factor in the reduced edema and congestion of the limb observed in experimental animals after partial arterial occlusion and syringe infusion of the chemotherapeutic agent. Clinically, when 2 or more perfusions may be deemed necessary to achieve full remission, the advantages of the simple perfusion are quite apparent. The sequela to chemotherapeutic failure in many chronic deep mycotic infections of the extremities is amputation and, accordingly, repeated arterial infusion must be considered seriously. The additional

features of simplicity with obviation of pump oxygenator apparatus seem to indicate that more detailed study and clinical trial are warranted. The application of the described technique to the treatment of chronic refractory bacterial infections or neoplasms of the extremities with appropriate chemotherapeutic agents requires further study.

The edema observed in a perfused extremity when 5 per cent dextrose and water was used as the perfusion vehicle substantiates the results obtained by Ryan when various crystalloid solutions were used. Preliminary experimental data from this laboratory have demonstrated a hemolytic effect of amphotericin B on whole blood when mixed and allowed to stand for 30 minutes at room temperature. A linear relationship exists between the amount of hemolysis and the quantity of drug added to the blood. Approximately 2,500 milligrams per cent of hemolysis was recorded when 25 milligrams of amphotericin B in 1 milliliter of 5 per cent dextrose and water were added to 5 milliliters of fresh heparinized dog blood. Only 175 milligrams per cent of hemolysis was measured when the serial dilution was carried down to 0.10 of a milligram of amphotericin B in 1 milliliter of dextrose and water which was added to 5 milliliters of blood. This observation suggests that varying amounts of the drug may be absorbed by red blood cells during perfusion if the drug concentration per unit of perfusate is considerably higher than in the conventional parenteral route of administration. Acellular perfusates presumably do not combine with the drug in this intimate manner at higher concentrations and, accordingly, provide a larger amount of irritative drug to the perfused intimal vascular linings and capillary beds with greater likelihood of subsequent edema. The absence of oxygen and carbon dioxide transfer in acellular perfusates is probably a major factor in producing edema after perfusion.

The application of the partial arterial occlusion and needle cannulation techniques to other areas of the body warrants further clinical investigation. Although such procedures may be considered quite heroic in areas less readily accessible than the extremity, the technique may be of considerable value as an adjunct to excision of cavitary pulmonary fungus disease. In advanced cancer when complete excision is not feasible, needle cannulation and syringe perfusion with carcinolytic agents may be of value as a simple adjunct to surgery. Larger doses of amphotericin B may be employed in the perfusate than were used in the clinical cases described, since it was demonstrated in the experimental studies that as much as 4 milligrams per kilogram of amphotericin B may be administered by pump oxygenator perfusion without notable injury to normal tissue. The isolated limb perfusion technique should be more efficacious in the treatment of localized advanced deep fungus infections when more effective chemotherapeutic agents become available.

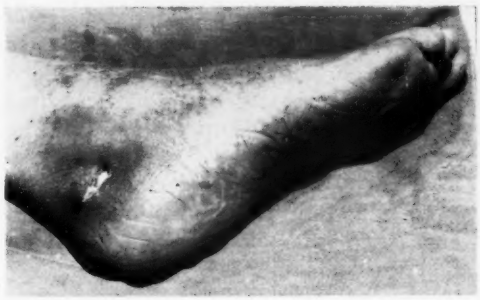


FIG. 10. Patient 4. Six weeks after isolation perfusion with amphotericin B.

SUMMARY

1. Amphotericin B has been effective in the treatment of early acute fungus infections; however, less favorable results have been obtained in deep chronic mycotic lesions of the extremities and other localized areas. Systemic toxic reactions of this drug occasionally preclude its use under present methods of administration.

2. Isolated organ perfusion techniques allow administration of high drug concentrations to the extremities while minimizing

the systemic toxic effects of the agent. This method was applied in 3 clinical cases of peripheral chronic fungus infection in which the pump oxygenator technique was used with the addition of amphotericin B to the perfusate.

3. Toxicity studies accompanying the intravenous administration of amphotericin B were carried out on dogs, and the minimum lethal dose was found to be 7 milligrams per kilogram of body weight. Systemic toxic manifestations were minimal in dogs whose hind extremities were perfused with lethal doses of amphotericin B.

4. A simple partial arterial occlusion and needle cannulation and infusion technique was carried out on isolated dog extremities and in 1 clinical case of peripheral coccidioidomycosis. This technique obviates the numerous difficulties which are associated with pump oxygenator perfusion, makes subsequent reperfusion more feasible, and is quite likely to be effective in future clinical trials.

REFERENCES

1. Beard, H. W., Richert, J. H., and Taylor, R. R. The treatment of deep mycotic infections with amphotericin B; with particular emphasis on drug toxicity. Am. Rev. Resp. Dis., 1960, 81: 43–51.
2. Creech, O., Jr., Krementz, E. T., Ryan, R. F., and Winblad, J. N. Chemotherapy of cancer; regional perfusion utilizing an extracorporeal circuit. Ann. Surg., 1958, 148: 616–632.
3. Halde, C., Newcomer, V. D., Wright, E. T., and Sternberg, T. H. An evaluation of amphotericin B in vitro and in vivo in mice against Coccidioides immitis and Candia albicans, and preliminary observations concerning the administration of amphotericin B to man. J. Invest. Derm., 1957, 28: 217–231.
4. Hottinger, G. C., Ryan, R. F., Delgado, J. P., and Reetsma, K. Physiology of extracorporeal circulation; studies of blood flow, oxygen consumption, and metabolism in the isolated and perfused extremity. Surgical Forum; Clinical Congress 1958. Vol. IX, pp. 80–82. Chicago: American College of Surgeons, 1959.
5. Mann, F. C., Herric, J. F., Essex, H. E., and Baldes, E. J. Effect on blood flow of decreasing lumen of a blood vessel. Surgery, 1938, 4: 249–252.
6. Ryan, R. F., Winblad, J. N., Hottinger, G. C., and Creech, O., Jr. Effects of various perfusates in isolated vascular beds using an extracorporeal circuit. Surgical Forum; Clinical Congress 1957. Vol. VIII, pp. 193–196. Chicago: American College of Surgeons, 1958.
7. Shingleton, W. W., and Parker, R. T. Abdominal perfusion for cancer chemotherapy using hypothermia and hyperthermia. Presented at the Annual Meeting of the Society of University Surgeons, February 9–11, Kansas City, Kansas.

EPIPHYSIAL STAPLING

ANTONI TRIAS, M.D., KARL MUELLER, M.D., and ROBERT D. RAY, M.D., F.A.C.S.,
Chicago, Illinois

LEG LENGTH INEQUALITY is a frequent disability in children and poses a real challenge to the orthopedic surgeon. According to Cameron, the problem was first recorded in Egypt in the eighteenth Dynasty when a prince was depicted in a mural with shortening of the right leg. Ollier was probably the first to attempt to retard growth surgically. In 1888, he resected the remaining portion of the distal epiphysis of the tibia to correct a traumatic varus deformity of the ankle. In 1933, Phemister reported operative arrest of longitudinal growth of bone for correction of leg length discrepancies. Phemister used a complicated growth chart to calculate the appropriate time for the operation, and at operation he curetted and grafted the epiphysial plate. It was claimed that the operation was of lesser magnitude than leg shortening procedures and did not carry as great a risk. Camera, in Italy, reported in 1924 resection of the epiphysial plate to arrest growth, but the method did not become widely accepted until Phemister's publication in 1933.

Interest in temporary arrest of epiphysial growth as a method for treating leg length inequality was stimulated by the experiments of Haas in 1945 in which growth was arrested by circling the epiphysial plate in dogs with a wire loop. Actually this was not a new procedure. In 1914 Arbuthnot Lane reported a fracture of the distal femoral epiphysis which he had fixed with 3 staples on the medial side. Subsequently genu varum developed as a result of growth arrest on the medial side.

Based on these reports Blount and Clarke (4) in 1949 proposed a simplified method for epiphysial arrest by inserting metal staples across the epiphysial line. The method was advocated as a technique for temporary arrest of growth. According to Blount (3) growth is retarded from 50 to 70 per cent during the first year and up to 90 per cent during the following years. It is claimed that this is a quantitative procedure, the amount of retardation depending on the number of staples inserted.

Blount's method has precipitated many arguments and stimulated many experimental studies. The two main areas of controversy are whether growth will resume at a normal rate after removal of the staples and how long the staples may be left in place without causing permanent arrest of growth.

Published results indicate that although growth may resume after removal of the staples, this cannot be predicted with certainty. Some workers have left them in place for as long as 4 years with resumption of growth after removal. Green and Anderson (14) have observed an open epiphysis after the staples had been left in situ for 4 years. Blount (1) states that it is usually not the length of time the staples are left in place but damage to the epiphysial plate during insertion or removal that causes permanent arrest.

Experimental evidence by Trueta and Trias suggests that under certain conditions the epiphysial plate may be severely and irreversibly damaged by pressure with formation of a bony bridge between epiphysis and metaphysis. However, it is difficult to correlate the results of animal experiments with clinical practice. In the experiments of Strobino, Colonna, and Brodey on the effect of compression on the growth of the

From the Department of Orthopedic Surgery, University of Illinois, College of Medicine, Research and Educational Hospitals and Presbyterian-St. Luke's Hospital, Chicago.

epiphysial plate in Holstein calves, it was found that the force necessary to arrest the proximal tibial epiphysis was 45 pounds per square inch and, with growth arrest for 7 months, marked shortening of the leg ensued. After release of the pressure, growth resumed immediately and was greatly accelerated. Eventually the limb length was practically equal to the opposite side. Blount (2) states that, in children, a temporary growth spurt may follow removal of staples but this is usually balanced by premature closure of the epiphyses at the end of the growth period.

In reviewing the cases of stapling at the University of Illinois, Research and Educational Hospitals, a high incidence of complications was encountered but in most cases these could be attributed to errors in preoperative planning, in surgical technique, or in the postoperative care. This article was undertaken to review some of the problems encountered in the hope that they might be avoided in the future.

PREOPERATIVE PLANNING

Preoperative planning in the case of leg length discrepancies is of critical importance and, unless properly carried out, even with excellent surgical technique and careful follow-up the end results will be disappointing. Several factors must be considered.

Etiology. The surgeon must decide whether he is dealing with functional or structural shortening or lengthening. If the leg length discrepancy is functional, i.e., fixed pelvic obliquity, hip deformity, or foot deformity, no attempt should be made to correct the difference in leg length until the primary deformity has been corrected whenever possible.

Structural leg length discrepancy has many causes. Congenital leg length inequality may or may not progress. Tumors such as neurofibromatosis or hemangiomas usually cause progressive disparity. As Trueta (23) has shown, infection of the metaphysis or diaphysis may result in increased growth. Infection or damage to the epiphysis, on the other hand, usually results in a decreased rate of growth. Poliomyelitis often causes progressive shortening but in other instances, as for example the shortening following some fractures, the discrepancy may be stationary. Thus, it is extremely important to consider the etiologic factors of the deformity in preoperative planning.

Prediction of growth. Successful permanent or temporary epiphysial arrest requires accurate prediction of future growth. Digby in 1916 published proportional growth figures for the different epiphyses based on measurements made of the distance of entrance of the nutrient artery from the ends of the long bones. He found that the upper femoral epiphysis contributes 15 per cent, the distal femoral 35 per cent, the upper tibial 30 per cent, and the distal tibial epiphysis 20 per cent to the total length of the leg. These figures, however, are not sufficiently accurate for prediction of relative growth rates. White and Stubbins concluded that the distal femoral epiphysis contributes $\frac{3}{8}$ inch and the proximal tibial epiphysis $\frac{1}{4}$ inch to the growth of the leg per year. Wilson and Thompson used the parent's leg length to compute the expected growth of the child's extremities. This, however, has proved to be inaccurate also. Gill and Abbott based their method on percentile measurements of a large number of normal children using the child's bone rather than chronologic age which makes the method much more accurate. Green's and Anderson's (13, 14) method is also based on bone age and careful anthropometric studies. The latter charts give the average expected growth for femur and tibia together with figures for standard deviations. The Green and Anderson charts are widely used in the United States and Europe but some investigators prefer the method outlined by Gill and Abbott.

Accurate planning, however, must also take into account the rate of growth of the affected leg. Although the etiology may be of some help, as already mentioned, the

growth rate may be very difficult to estimate. Stinchfield, Reidy, and Barr found that in poliomyelitis there is a definite relationship between relative muscle strength and the discrepancy in limb length. Although prediction of growth or lack of growth is subject to wide variation, these workers suggested that clinical application should be made of the relationship between muscle power and leg length discrepancy. To predict the rate of growth they suggest that muscle evaluation be carried out by Lovett's method 2 to 3 years after onset of poliomyelitis; continued growth in length frequently occurs during the first year. By use of their table, shortening of the lower extremity can be predicted from examination of the muscle of the involved extremity.

Length measurements of the lower extremities. For clinical evaluation it is best to measure from the anterosuperior iliac spine to the medial malleolus or, still better, to the heel with the patient standing. Measurements of the long bones by roentgenograms will give more accurate estimates of the actual length but the effect of other deformities on the patient's gait, such as equinus or calcaneous deformities and deformities of the hip or knee, cannot be evaluated by roentgenograms alone.

The accuracy of leg length measurements has also been the subject of controversy. Ordinary roentgenograms are unreliable. Teleroentgenograms are better provided that the tube film distance is constant from one film to the next for a given patient. The method currently used at the University of Illinois is to take spot films of the hip, knee, and ankle with a graded metallic ruler applied longitudinally to the leg. This is a modification of the spot orthoroentgenographic method described by Goldstein and Dreisinger. The disadvantages of this method are: (1) A flexion contracture of the hip or knee may result in false shortening. This can be avoided by placing the other leg in the same amount of flexion as the involved leg. (2) The tube may not be centered over the same point on the right and left leg and hence discrepancies in projection may arise. (3) When the film is poorly exposed, too light or too dark, the gradings of the metallic ruler cannot be read. (4) On moving the tube from the hip to the knee and to the ankle, the patient or the ruler may inadvertently move.

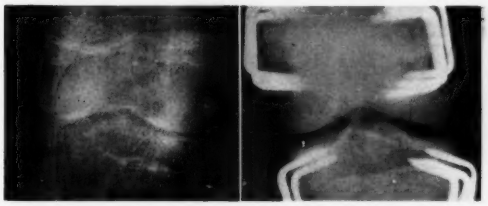


FIG. 1. Roentgenogram of both knees showing closure of the femoral and tibial epiphyses 1 year after stapling on the left side.

Teleroentgenograms should be made by experienced x-ray technicians and preferably by the same technician each time.

In order to obtain adequate evaluation of the rate of growth it is necessary to get at least 3 teleroentgenograms at 3 to 4 month intervals before operation. For research purposes films are also valuable during the postoperative period, and for accuracy metallic markers should be introduced at the time of operation as advised by Blount (1).

If the foregoing factors are not carefully evaluated during the preoperative period, complications such as those illustrated by the following case histories are bound to occur.

A child had poliomyelitis at the age of 2 years with resultant progressive shortening of the right leg. At the age of $9^{10}/_{12}$ years, when the bone age was 8 years, a discrepancy of 1.5 centimeters was present. Stapling of the distal femoral epiphysis on the left side was carried out. Fifteen months later this leg was 3 millimeters shorter than the right leg and the staples were removed. When the patient was seen again 8 months after removal of the staples, the left leg was 2.5 centimeters longer than the right.

The discrepancy should have been corrected according to the amount of shortening expected by the end of the patient's growth period.

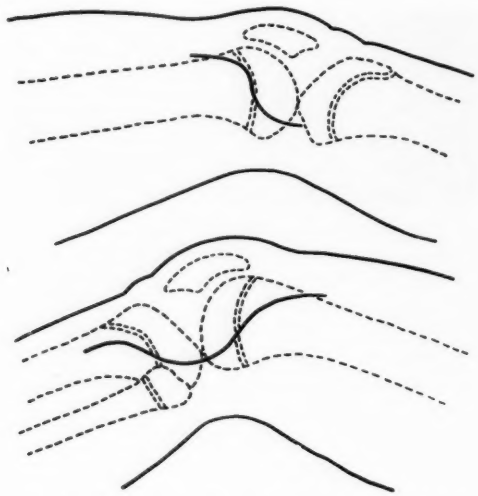


FIG. 2. Sketches to illustrate skin incisions used in epiphysial stapling: the upper for the distal femoral epiphysis, the lower for the combined approach to the distal femoral and proximal tibial epiphyses and for the curettment of the fibula (Blount's technique).

Another error encountered was evaluation of the patient on the basis of chronologic rather than skeletal age. Differences of as much as 2 years between chronologic and skeletal age have been observed.

A girl had poliomyelitis at the age of 6 years which resulted in shortening of the right leg of 3.8 centimeters by $11\frac{8}{12}$ years of age. The bone age was not evaluated. The distal femoral and proximal tibial epiphyses were stapled. One year later all epiphyses were closed and no correction had been obtained (Fig. 1). The patient's bone age was probably more advanced than the chronologic age.

The patient had poliomyelitis at 2 years of age with 3.5 centimeters of subsequent shortening of the left leg. The right upper tibial and distal femoral epiphyses were stapled when the patient was 13 years old. The epiphyses closed shortly after stapling and the discrepancy remained at 3.5 centimeters.

Here again, skeletal age was not determined preoperatively. Permanent arrest of growth (epiphysiodesis) or, better, a shortening osteotomy at the end of the growth period would have been preferable.

A boy had hemihypertrophy involving the right side. At the age of 14 years the right leg was 6.1 centimeters longer than the left. No preoperative studies of the rate of bone growth or bone age were made. The distal femoral epiphysis and proximal tibial epiphysis were stapled. Two years later all epiphyses were closed and a residual shortening of more than 3 centimeters was still present.

In this case epiphysiodesis of both epiphyses would have been the method of choice.

Stapling performed at the time indicated by growth charts will result in inadequate correction because stapling only retards but does not arrest growth. The main advantage of stapling over epiphysiodesis is that one can correct leg length discrepancies at an earlier age according to Blount (2); however, stapling should not be performed before the patient is 8 years of age. Another advantage of stapling is that it allows errors in prediction of growth to be corrected by removal of staples provided growth resumes.

SURGICAL TECHNIQUE

The surgical technique of stapling is not easy. Meticulous attention to detail is absolutely necessary for a successful result. The procedure has been described by Blount (1, 5) as follows: with the patient under general anesthesia, the leg is prepared and draped and a tourniquet is applied to the thigh. The knee is flexed approximately 60 degrees over a wooden block or folded sheet to facilitate exposure of the posterior epiphysial line. The skin incisions are shown in the drawing (Fig. 2).

The underlying fascia is split in the direction of its fibers, and the muscles are retracted—muscles have to be split only on the lateral side of the proximal tibial epiphysis. Thus the periosteum is exposed. The epiphysis is then located by reference to roentgenogram of the knee and palpation of the bony landmarks. The periosteum is not stripped, and the epiphysial line should not be exposed. Locating the epiphysial disc with a needle may be helpful in older children, but in younger children the bone and the epiphysial plate have approximately the same consistency, and this method is not of much help.

Three or 4 staples are then inserted on

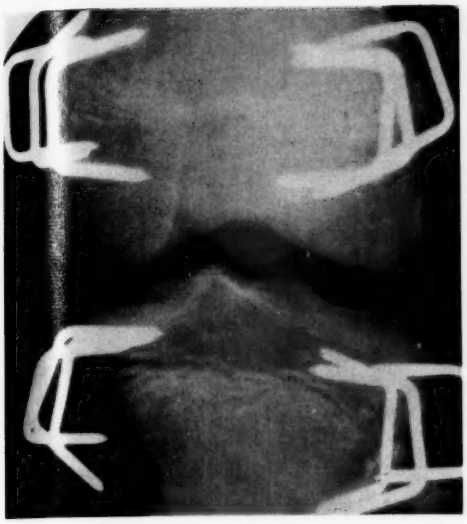


FIG. 3.

FIG. 4.

FIG. 3. Roentgenogram of knee showing extrusion of staples 18 months after insertion with spreading of some.
FIG. 4. Roentgenogram of distal femoral epiphysis shows spreading of old type staples 2 years after operation.

each side of the epiphysial plate according to the age of the child and the amount of retardation desired. Care should be taken to place the posterior staple back far enough and the anterior staple far enough anteriorly. The staples should be directed toward the center of the bone. This is particularly important in the case of the posterior staples to avoid driving them into the popliteal space. A roentgenogram is taken to check the position of the staples. Poorly placed staples should be reinserted but the poorly placed staple may be used as a guide for the new staple. When all staples are in satisfactory position they are driven in completely. Occasionally one staple extrudes while another is driven in. The periosteum should be incised under the cross bar of each staple before driving it home to avoid pain from the soft tissues. The staples should not be driven in too deeply and they should not be buried under the periosteum.

The upper fibular epiphysial plate should not be stapled but rather curetted when the proximal tibial epiphysis is stapled. This can be accomplished by splitting the fascia just anterior to the head of the fibula and then splitting the fibula so that it may be opened like a book. Thus the peroneal nerve is protected. However, it is usually safer to expose the nerve to avoid injury. In 1 of our patients, the nerve was not identified and there was a temporary peroneal nerve paralysis. Another instance of this complication has been reported by Mosheim. The fibular epiphysial plate is curetted and the head of the fibula replaced in its original position. After all staples have been checked by a final roentgenogram the wound is closed and a plaster cylinder is applied for 3 weeks. Several complications may occur as the result of faulty surgical technique. If the epiphysial plate is exposed in attempting to locate it, it can be damaged and partial or complete growth arrest can result. Stripping the periosteum may result in bony proliferation with formation of a bony bridge across the epiphysis. Staples that are covered by bone are extremely difficult to remove, and the epiphyses can be damaged when the staples are removed with subsequent complete arrest of growth.

A male had poliomyelitis at the age of 3 years. At the age of 12, the leg length discrepancy was 2.5 centimeters, the left leg being shorter. The right upper tibial and the lower femoral epiphyses were stapled.

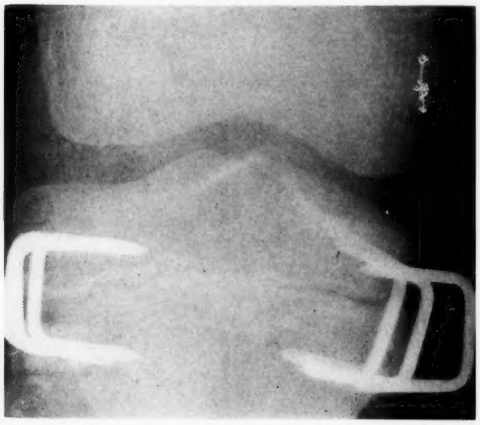
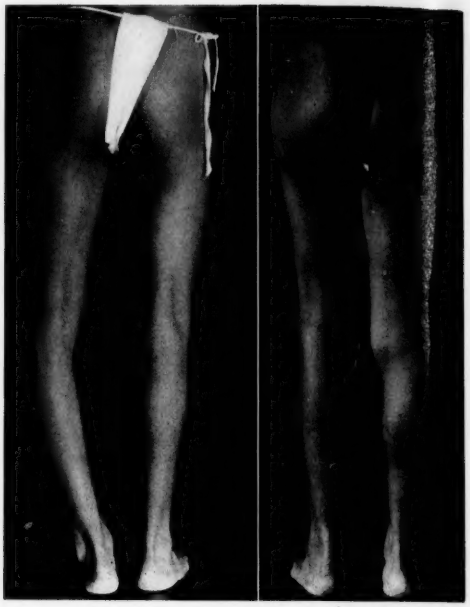


FIG. 5.

FIG. 6.



a b

FIG. 7.

FIG. 5. Anteroposterior view of the proximal tibial epiphysis illustrating extrusion of staple on the medial side of the upper tibial epiphysis necessitating replacement.

FIG. 6. Roentgenogram of the proximal tibial epiphysis showing 2 staples broken on the lateral side with development of genu varum.

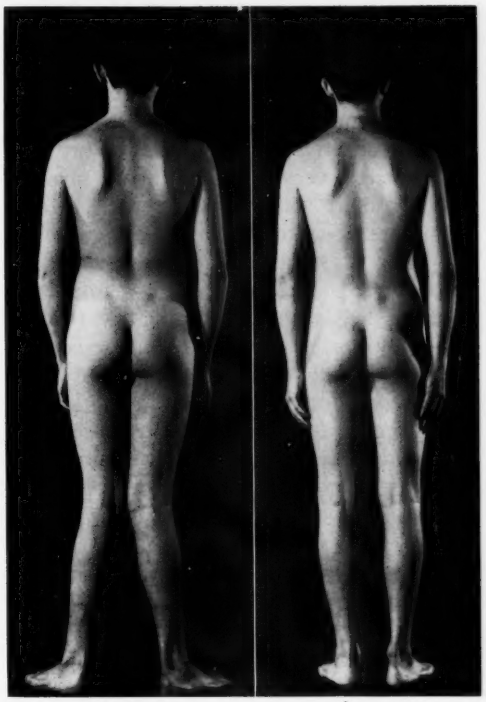
FIG. 7. Photograph showing: a, genu varum deformity which occurred after stapling the left proximal tibial epiphysis; b, after osteotomy and resection of the upper tibial epiphysial plate, the left leg remains longer.

During the operation the periosteum was incised and stripped. The staples were removed 2 years later. They were found to be completely covered by bone and were extremely difficult to remove. Growth did not resume after removal of the staples and overcorrection resulted. The leg that was operated on is now 2 centimeters shorter than the opposite leg.

Poor placement of the staples can result in a number of deformities. If the staples are placed too far anteriorly, back knee will result from overgrowth of the posterior part of the epiphysis. Posterior placement of the staples will result in a flexion deformity but this is rare because it is difficult to get staples too far posteriorly. Knock knee or bowleg may result from poor placement or extrusion of the staples on one side of the epiphysis. This is especially true in the case of the proximal tibial epiphysis. The tibia tubulates abruptly just distal to the epiphysis and it is difficult to insert the staples so that the proximal and distal legs of the staples have an equal hold on the bone. Since the upper tibial epiphysis tubulates in the absence of growth, the distal leg of a well placed staple may extrude from the bone.

A boy had chronic osteomyelitis of the right femur after a gunshot wound in infancy, and at the age of $11\frac{8}{12}$ years the right leg was 6.2 centimeters shorter than the left. The distal femoral and the proximal tibial epiphyses were stapled. A roentgenogram taken 18 months after operation showed that 2 of the staples were bent, and 1 was not, indicating that the staple that was not bent was not in the bone (Fig. 3). A valgus deformity of the knee of 30 degrees developed requiring osteotomy of the upper tibia and later a supracondylar osteotomy of the femur.

A girl had poliomyelitis at the age of 1 year. At the age of 8 years, 5.6 centimeters of shortening had developed in the left leg. Stapling of the right femoral epiphysis was performed with an old style staple. Two years later the staples had to be changed for a newer, heavier type because as growth occurred the staples had spread and little correction had been obtained (Fig. 4). Both the upper tibial and the lower femoral epiphyses were stapled at the time the staples in the lower femoral epiphysis were exchanged. When the staples were removed, at which time the patient was 12 years old, they were completely buried by bone with permanent arrest of growth of these epiphyses whereas the other epiphyses were still open. The left leg was 2 centimeters shorter and there was 30 degrees of genu recurvatum.



a b

FIG. 8. Photograph illustrating: a, bilateral genu valgum before correction by stapling the medial side of the distal femoral epiphyses bilaterally; b, correction of the deformity by the end of the growth period.

POSTOPERATIVE PERIOD

Patients must be followed up carefully after epiphysial stapling. They should be seen at least every 3 months during the first year and every 6 months thereafter. Roentgenograms need not be taken at every visit but a roentgenogram should be taken at the first postoperative visit to determine the position of the staples and to see if any has extruded or broken. Beginning deformities can be detected by physical examination; extruded, broken, or poorly placed staples should be replaced before deformity develops.

A male had congenital hypertrophy of the left leg which resulted in a shortening of the right leg of 4.9 centimeters by the time the patient was $10\frac{9}{12}$ years old. Stapling of the upper tibial epiphysis on the left side was performed, 3 staples being placed in each side. One year later, 1 staple on the medial side had extruded and had to be replaced (Fig. 5). Afterward a genu varum deformity of 30 degrees developed before new roentgenograms were taken. These showed 2 broken staples on the lateral side and complete extrusion of the distal legs of all lateral staples (Fig. 6). The deformity had to be corrected by osteotomy and excision of the epiphysial plate (Fig. 7). This method, however, failed to correct the leg length discrepancy.

Staples should be removed when a good cosmetic result has been obtained, not when roentgenograms show complete correction. In some cases associated with drop foot, weak abductors of the hip, stiff hip, or stiff knee, complete correction is frequently undesirable. Linear discrepancies should not be overcorrected, except in cases in which the leg length discrepancy is progressive. In such cases the correct time for removal of the staples should be determined by the preoperative growth rate evaluation. Removal of the staples will cause slight acceleration of growth which will make the stapled leg temporarily longer. However, a stapled epiphysis closes earlier—6 months to a year according to Green and Anderson (14)—

than the epiphysis on the other side, and the discrepancy caused by the growth spurt will be corrected eventually.

Patients who have had epiphysial stapling for knock knee or bowleg deformities should be observed even closer. Angular deformities may correct very rapidly during growth. They should be overcorrected slightly because removal of the staples will cause acceleration of growth on the stapled side for a short period. Correction of angular deformities by unilateral stapling gives excellent results, is less traumatic than correction by osteotomy, and allows the patient to be ambulatory during treatment. Knock knee or bowleg in a short leg, however, is better corrected by osteotomy which stimulates growth than by stapling which retards it.

A 12 year old boy had bilateral congenital genu valgum. At the age of 12 years, 3 staples were inserted in the medial side of the distal femoral epiphysis in both legs. The staples were removed 2½ years later with an excellent result. At the last clinic visit all of the patient's epiphyses had closed, and complete correction of the deformity had been maintained (Fig. 8).

DISCUSSION AND CONCLUSIONS

At the University of Illinois, Research and Educational Hospitals, 17 patients have been studied after stapling—1 had bilateral stapling. As a result of mistakes in preoperative planning, surgical technique, or because of inadequate follow-up, 6 osteotomies for knee deformities and 2 femoral shortenings at the end of the growth period had to be performed. The number of complications is extremely high when compared with other series. Green and Anderson (14) reported 35 per cent complications in 83 cases, and in general the complications were not as serious.

In nearly 200 cases, Blount (1) reported 2 bowlegs, 4 knock knees, and 2 back knees. Only 1 osteotomy had to be performed. Mosheim reported only minor complications in 52 consecutive cases. Brockway, Craig, and Cockrell reported a high incidence of serious complications following stapling. Blount's (1) comment in discussing the latter article may apply to this one, "In all fairness, the title of this paper should have been, 'Technical Errors Which We Made in the Stapling Operation'."

This article is intended to illustrate the fact that the treatment of leg length discrepancies by stapling involves many factors. Unless attention to detail is meticulous during each of the three stages of treatment, the end results will be disappointing. Preoperative planning includes: adequate evaluation of growth based on bone age rather than chronologic age and careful calculation of the remaining growth potential. There has been a tendency to perform stapling too late with resultant inadequate correction. In these cases epiphysiodesis is preferred. Stapling performed at the time indicated by growth charts does not give satisfactory correction because stapling does not arrest growth completely. Surgical technique must be meticulous. If the epiphysial plate is traumatized during surgery, the periosteum stripped, or the staples buried, new bone formation over the staples can cause deformities or even complete arrest of growth. Poor placement of the staples may cause angular deformities of the knees. The fact that most of our complications occurred after stapling the proximal tibial epiphysis re-emphasizes a warning given by Blount (2) in 1958 and Green and Anderson (14) in 1957 concerning stapling this epiphysis. The shape of the upper tibia and the mechanism of remodelling make this a hazardous site for staples.

Careful follow-up is necessary during the postoperative period to detect developing deformities. These can be corrected easily by reinsertion of the staples. If the patient is not followed up carefully, deformities may become severe enough to warrant corrective osteotomies. The effectiveness of staples depends on the rate of growth of the opposite leg. If little growth takes place while the staples are in situ little correction is obtained, and in such cases the staples must be left in longer.

In conclusion, both epiphysiodesis and stapling have a place in the treatment of leg length discrepancies, and when properly performed the complications which have been reported may be avoided.

REFERENCES

1. Blount, W. P. Discussion. J. Bone Surg., 1954, 36-A: 1069–1070.
2. Idem. Unequal leg length in children. Surg. Clin. N. America, 1958, 38: 1107-1123.
3. Idem. Personal communication, 1960.
4. Blount, W. P., and Clarke, C. R. Control of bone growth by epiphyseal stapling; a preliminary report. J. Bone Surg., 1949, 31-A: 464–468.
5. Blount, W. P., and Zeir, F. Control of bone length. J. Am. M. Ass., 1952, 148: 451–457.
6. Brockway, A., Craig, W. A., and Cockrell, B. R. End result study of 62 stapling operations. J. Bone Surg., 1954, 36-A: 1063–1069.
7. Camera, U. À propos de l'epiphisiodhese (Beitragzur Epiphysiodese.) Deut. Orth. Ges. Verhandl., 40 Kongress 1952, 212.
8. Cameron, B. M. Leg length inequality. Orthopaedics, 1959, 1: 67.
9. Digby, K. H. The measurement of diaphyseal growth in proximal and distal directions. J. Anat., Lond., 1916, 50: 187–188.
10. Gill, G., and Abbott, L. C. Practical method of predicting the growth of the femur and tibia in the child. Arch. Surg., 1940, 45: 286–315.
11. Goldstein, L. A., and Dreisinger, F. Spot orthoroentgenography; a method for measuring the leg length of the bones of the lower extremity. J. Bone Surg., 1950, 32-A: 449–452.
12. Green, W. T., and Anderson, M. Experiences in the epiphyseal arrest in correcting discrepancies in length of the lower extremities in infantile paralysis. J. Bone Surg., 1947, 29: 659–675.
13. Idem. Discrepancy in length of the lower extremities. Instructional course lectures. Am. Acad. Orthop. Surg., 1951, 8: 294–305.
14. Idem. Epiphyseal arrest for the correction of discrepancies in length of the lower extremities. J. Bone Surg., 1957, 39-A: 853–872.
15. Haas, S. L. Retardation of bone growth by a wire loop. J. Bone Surg., 1945, 27: 25–36.
16. Lane, A. The Operative Treatment of Fractures. 2nd ed., p. 133. London: Medical Publishing Co., 1914.
17. Lovett, R. W. The Treatment of Infantile Paralysis. 2nd ed., p. 132. Philadelphia: Blackiston's Son & Co., 1917.
18. Mosheim, Y. Epiphyseal arrest with staples, follow-up of 52 cases. J. Bone Surg., 1957, 39-A: 449–450.
19. Ollier, L. Traite des resections et des operations conservatrices qu'on peut practiquer sur le systeme osseux. 5th ed. Vol. II, p. 473. Paris: V. Masson, 1888.
20. Phemister, D. B. Operative arrestment of longitudinal growth of bones in the treatment of deformities. J. Bone Surg., 1933, 15: 1–15.
21. Stinchfield, A. J., Reidy, J. A., and Barr, J. S. Prediction of unequal growth of the lower extremities in anterior poliomyelitis. J. Bone Surg., 1949, 31-A, 478–486.
22. Strobino, L. J., Colonna, P. C., Brodey, R. S., and Leinbach, T. The effect of compression on the growth of the epiphyseal bone. Surg. Gyn. Obst., 1956, 103: 85–93.
23. Trueta, J. Influence of blood supply in controlling bone growth. Bull. Hosp. Joint Dis., N. Y., 1953, 14: 147–157.
24. Trueta, J., and Trias, A. The vascular contribution to osteogenesis; the effect of pressure upon the epiphyseal cartilage of the rabbit. J. Bone Surg., Brit. ed., to be published.
25. White, J. W., and Stubbins, S. G., Jr. Growth arrest for equalizing leg length. J. Am. M. Ass., 1944, 126: 1146–1148.
26. Wilson, P. D., and Thompson, T. C. A clinical consideration of the methods of equalizing leg length. Ann. Surg., 1939, 110: 992–1014.

PROPAGATION OF INDUCED VENOUS THROMBI

R. RANDOLPH BRADHAM, M.D., F.A.C.S., Charleston, South Carolina

PERIPHERAL VENOUS THROMBOSIS continues to be one of the most catastrophic postoperative complications. It results in either death by thromboembolism or devastating venous occlusion of the lower limbs. Present diagnostic and therapeutic measures are inadequate. Anticoagulants are widely accepted as the most effective agents with which to manage thrombophlebitis, phlebothrombosis, and thromboembolism. These agents aid in retarding further propagation of a thrombus which has already formed. Fibrinolysin infusions have recently been publicized as a means of dissolving fresh thrombi. Our own experiments (1, 3) have failed to support the dissolution properties of this enzyme.

Only through studying the characteristics of thrombosis can we hope to achieve more effective means of managing thrombotic disease states. Factors which are extremely important are the rapidity of thrombus propagation after initiation and the extent of propagation without treatment.

This laboratory study includes 44 animal experiments designed to investigate thrombosis. The results indicate that thrombus propagation is rapid and is limited by the size of the area of tissue injury created to produce these thrombi. Clinical applications of this study are suggested.

METHOD

Venous thrombi in the right femoral vein of mongrel dogs were produced at the positive electrode by passing a 10 milliampere current through the vein wall for 1 hour. This technique is a modification of that described by Williams and Carey (4). Forty-four dog experiments were performed. Groups of animals were sacrificed at periods varying from 6 hours to 20 days after thrombosis. Ten dogs were sacrificed 6 hours after removal of the electrodes, 5 dogs at 24 hours, 5 dogs at 48 hours, 5 dogs at 3 days, 5 dogs at 4 days, 5 dogs at 5 days, 4 dogs at 10 days, and 5 dogs at 20 days postthrombosis. The lower inferior vena cava, iliac, and femoral veins were removed in continuity and opened to evaluate extent of thrombus propagation. The specimen removed was photographed so that comparative observations could be made.

RESULTS

There were thrombi present in all dogs with the exception of 3 in the 20 day group. In the dogs sacrificed at 6 hours, thrombi were present which were slightly smaller than those in dog's sacrificed after a longer interval (Fig. 1). The thrombi present in the dogs sacrificed at 24 and 48 hours were as large as those found in any of the dogs in this series (Fig. 2). There was no further increase in size of the thrombi in dogs sacrificed at 3, 4, and 5 days after thrombosis. (Fig. 3). Thrombi present in dogs sacrificed at 10 and 20 days after thrombosis were smaller than those seen in the early periods. The veins in several were attenuated and some actually disrupted (Fig. 4).

There were no deaths in the entire series prior to sacrifice date nor was there any clinical evidence that any dog sustained a pulmonary embolus. The lungs were not examined routinely at autopsy.

DISCUSSION

The thrombi formed in these experiments could be due to an attraction of negatively

From the Department of Surgery, Medical College of South Carolina, Charleston.

Supported by a grant from the United Health and Medical Research Foundation of South Carolina.

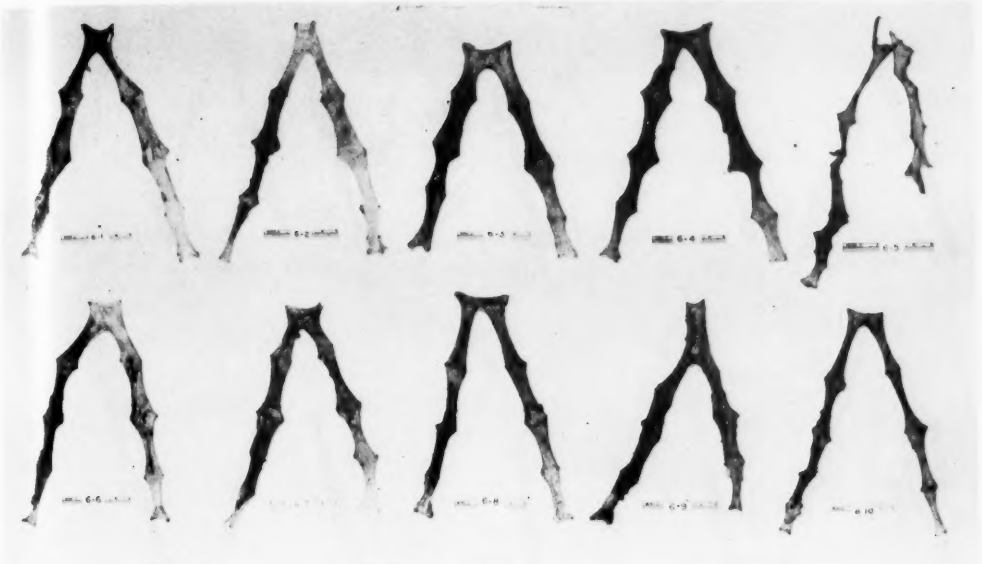


FIG. 1.

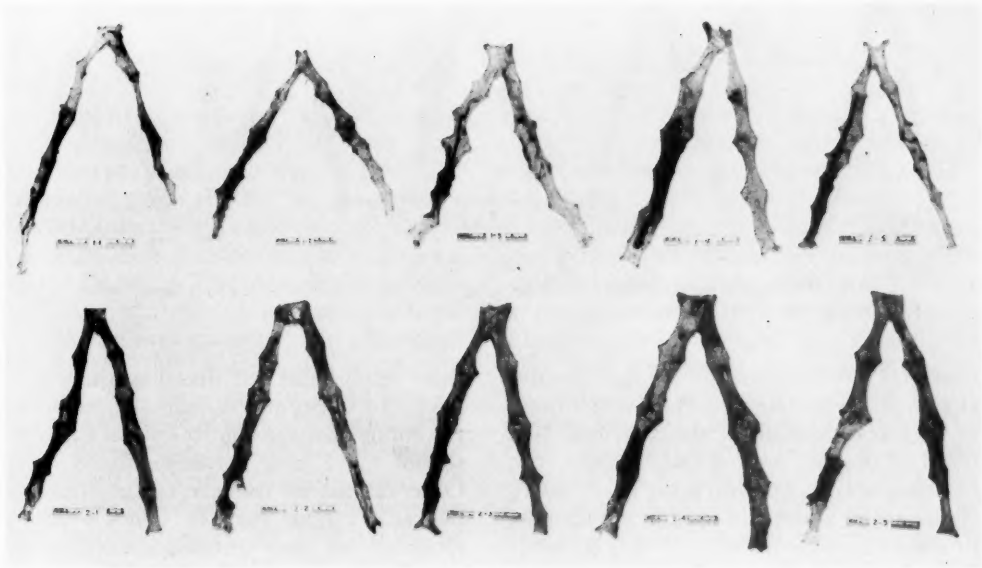


FIG. 2.

FIG. 1. Thrombi in right femoral veins 6 hours after induction.
FIG. 2. Thrombi in right femoral veins 24 hours, top row, and 48 hours, bottom row, following induction.

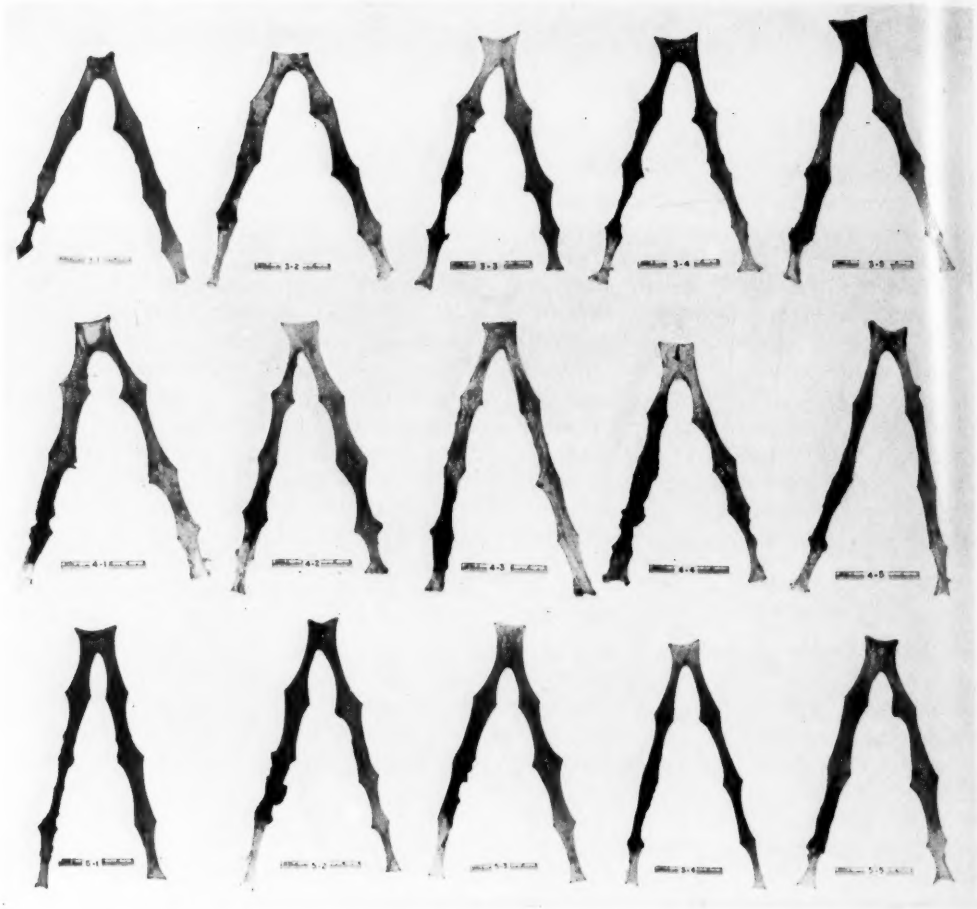


FIG. 3. Thrombi in right femoral veins 3 days, top row, 4 days, middle row, and 5 days, bottom row, after induction of thrombi.

charged blood elements to the positive electrode, to an area of vein wall injury, or to a combination of these factors. It is believed that an area of tissue injury with release of thromboplastin is the major factor contributing to the initiation of the thrombi in these experiments as there was certainly injury to the vein wall. This damage was more marked where the positive electrode contacted the vein as demonstrated in Figure 5.

The rapidity with which thrombus propagation occurred in these experiments is most remarkable. Similar experiments reported by Carey and Williams demonstrated thrombus propagation to several times the size of the 1 hour thrombus at 48 hours. Observations on the size of the thrombus between 1 hour and 48 hours were not recorded by these investigators. The important aspect of this early propagation clinically is that for anticoagulant therapy to be effective, it must be instituted almost immediately after initiation of a thrombus. It is true that in thrombophlebitis of a superficial vein, thrombosis progresses rela-

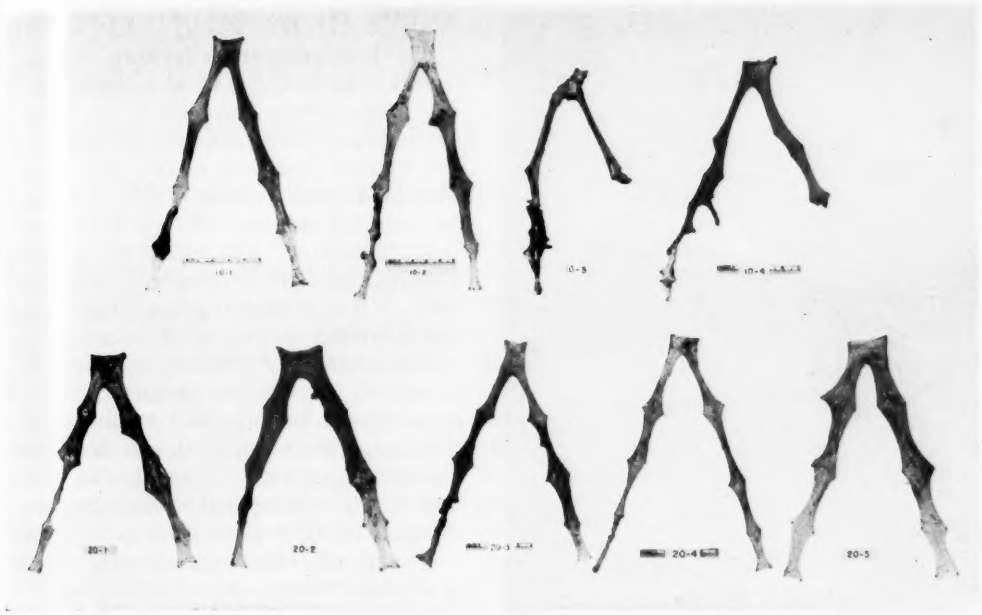


FIG. 4. Thrombi in right femoral veins 10 days, top row, and 20 days, bottom row, after induction of thrombi.

tively slowly. This fact, however, could be due to involvement of the vein with fresh thrombus formation at the site of progressive tissue damage and not due entirely to propagation of the initial thrombus. Our studies show that the original thrombus attains a definitive size rapidly and that it is at maximum size at the end of 24 to 48 hours. The thrombi in the dogs sacrificed at later intervals contained thrombi that were no larger. The absence of thrombi and the smaller sizes of thrombi present in the dogs studied at 10 and 20 days are indicative of both clot organization and retraction and also of the existence of some naturally occurring thrombolysin. The attenuation and destruction of the veins in these particular dogs are believed to be the result of the tissue damage which occurred during the course of the induction of the thrombus.

Any attempt to project such a laboratory study into a clinical situation occurring in man obviously has many disadvantages. On the other hand, such a direct study cannot be carried out on individuals with thrombophlebitis. Therefore, studies of this type must leave us with certain suggestions which might aid in re-evaluation of present methods of therapy.

Certainly, the most effective anticoagulant available to initiate therapy is heparin as a state of blood hypocoagulability can be produced immediately by its intravenous administration. Williams and Elliott (5) were able to prevent thrombus propagation with heparin when the Lee and White clotting time was elevated to at least 1½ times the preheparin level. Failure to maintain this elevated clotting time allowed thrombus propagation. Dicumarol, tromexan, and coumadin were ineffective unless held at dangerously low levels. Because there is usually delay in making a diagnosis of thrombophlebitis, during which delay the thrombus is propagating rapidly, more thought and study might be given to removal of the thrombus immediately and

FIG. 5. Microscopic section, × 121, of thrombus attachment to vein wall 6 hours after thrombosis. Note vein wall damage.

thereafter to initiating and maintaining a state of blood hypocoagulability with heparin.

At the present time, studies are being carried out in our laboratory to determine what protective effect the enzyme fibrinolysin might have on limiting thrombus propagation.

SUMMARY AND CONCLUSIONS

This laboratory study includes 44 animal experiments designed to investigate thrombus propagation. Thrombosis was induced by passing a 10 milliampere current through the femoral vein wall of dogs for 1 hour. Groups of dogs were sacrificed at intervals between 6 hours and 20 days after thrombosis. Rapiditity and extent of thrombus propagation were determined. The results indicate that thrombus propagation is rapid and is limited by the size of the area of vasculitis created to produce these thrombi. This study suggests that for present methods of therapy to be effective, a state of blood hypocoagulability must be effected immediately upon making a diagnosis of thrombophlebitis as delay will allow for rapid extension of the thrombus. Presently this state can be effected best by intravenous infusions of heparin.

REFERENCES

1. BRADHAM, R. R., and LEE, W. H., JR. Dissolution effect of human fibrinolysin on preformed venous thrombi in dogs. Surg. Gyn. Obst., 1961, 112: 295.
2. CAREY, L. C., and WILLIAMS, R. D. Comparative effects of dicoumarol, tromexan, and heparin on thrombus propagation. Ann. Surg., 1960, 152: 919.
3. LEE, W. H., JR., and BRADHAM, R. R. Evaluation of the dissolution effect of fibrinolysin (plasmin) on induced vascular micro thrombi; a direct approach. Surgery, in press.
4. WILLIAMS, R. D., and CAREY, L. C. Studies in the production of "standard" venous thrombosis. Ann. Surg., 1959, 149: 381.
5. WILLIAMS, R. D., and ELLIOTT, D. W. The effects of heparin and coumarin derivatives on a standardized intravenous thrombosis. Surgical Forum; Clinical Congress 1958. Vol. IX, p. 138. Chicago: American College of Surgeons, 1959.

THE EFFECTS OF ACID EXTRACT OF COLLAGEN, COLD NEUTRAL SOLUTIONS OF COLLAGEN, AND RECONSTITUTED COLLAGEN FIBRILS ON WOUND HEALING IN NORMAL AND PROTEIN-DEPLETED RATS

ERLE E. PEACOCK, JR., M.D., F.A.C.S., Chapel Hill, North Carolina

A WORKING CONCEPT for the production of collagen in healing wounds can be expressed as follows: Proline→hydroxyproline →saline extractable collagen→acid extractable collagen→mature insoluble collagen. Although there is some disagreement over the exact site of production of the collagen fibril, it is virtually certain that the conversion of proline to hydroxyproline and the synthesis of the basic collagen molecule occur as an intracellular function of mature fibroblasts. It is not certain, however, whether fibroblasts secrete a monomeric collagen molecule which polymerizes outside of the cell to form fibrils or whether small fibrils are actually formed within the cell and are secreted into the extracellular space. The preponderance of evidence, however, supports the theory that fibril formation occurs by the polymerization of monomeric building blocks on the external surface of the cell membrane.

The earliest known extracellular precursor of collagen has been described by Gross, Highberger, and Schmitt (2) as being a macromolecule which measures approximately 15 by 3,000 angstroms and which is characterized by being soluble in .45 molar saline. Saline extractable collagen is referred to as tropocollagen and differs from procollagen, described by Orekhovitch, in that procollagen is soluble in citrate but is not soluble in saline. Procollagen is probably not the basic building block for collagen fibrils, as Orekhovitch suspected, but is, instead, a very early polymerization product which is still soluble in a strong salt solution. Under the influence of the ionic strength, *p*H, and temperature of the ground substance, tropocollagen particles polymerize by the formation of secondary hydrogen bond cross-links, by van der Waals' forces, and by electrostatic bonds between charged groups to produce collagen fibrils which have a repeating axial period of 640 angstroms.

Recently, a laboratory experiment has been used by Gross and others (3) to study certain aspects of the in vitro polymerization of tropocollagen. This experiment, which is somewhat analogous to the extracellular phase of in vivo collagen production, is as follows: An acid solution of collagen, prepared by extracting calf dermis with .5 molar acetic acid, is filtered until it is clear. Such a solution is very viscous because of the dissolved collagen, but examination by electron microscopy does not reveal any collagen fibrils. The clear, highly viscous solution can be dialyzed against a cold phosphate buffer until the *p*H has been restored to neutral, but as long as the temperature remains below 8 degrees C. the collagen solution will be clear because polymerization does not occur at this temperature regardless of the *p*H. When the cold neutral solution is warmed to 37 degrees C., however, a firm gel will develop within 20 minutes. Examination of this gel under the electron microscope reveals typical fibrils

From the Department of Surgery, University of North Carolina School of Medicine and the North Carolina Memorial Hospital, Chapel Hill, North Carolina.

Supported by Grant No. A-2777 and Grant No. A-3664 from the National Institute of Arthritis and Metabolic Diseases, Public Health Service, Bethesda, Maryland.

which are indistinguishable from native collagen.

In certain abnormal conditions, such as protein deficiency and scurvy, in which delayed wound healing is characterized by diminished collagen production, at least one of the basic defects appears to be a failure of the cells to hydroxylate proline. Wound tissue from animals with protein deficiency shows an elevated level of proline and a diminished level of hydroxyproline. Because the amino acid composition of tropocollagen is essentially the same as that of mature collagen, one would not expect to find a reversal of the proline-hydroxyproline ratio if the primary defect in healing was in either the extracellular or the polymerization phase.

In previously reported experiments (6), it was shown that the hydroxylation of proline cannot be bypassed by loading an animal with hydroxyproline. Apparently, free hydroxyproline is not an intermediate in the production of collagen, and externally administered hydroxyproline is excreted almost quantitatively.

If the rate of gain in tensile strength of healing wounds is proportional to the rate of production of tropocollagen particles and if the inability to produce tropocollagen is the only defect in retarded wound healing, it was hypothesized that it might be possible to influence favorably healing in both normal and abnormal animals by flooding their wounds with various forms of monomeric collagen precursors or freshly reconstituted collagen fibrils. From the reconstitution experiment described, 3 types of collagen can be obtained for this purpose—acid extractable, cold neutral, and freshly reconstituted.

Experiments were designed to evaluate these 3 types of collagen on the healing process in normal and protein-depleted rats.

MATERIALS AND METHODS

Preparation of collagen. Acetic acid extractable collagen was prepared in the following manner. The tail tendons from approximately 30 rats were coarsely minced with fine scissors. The tendon fragments were washed in several changes of cold distilled water and allowed to remain in cold water overnight. The thoroughly washed fragments of collagen were then extracted with 1 liter of .5 molar acetic acid in a 5 degree C. cold room for 2 days. The highly viscous extract was filtered through coarse and fine sintered glass filters until it was clear. Clear acid extracts of rat tail collagen can be stored for 6 months at 5 degrees C. or they can be lyophilized and kept indefinitely. In these experiments, the acid extract was lyophilized immediately and the fluffy, white material which was obtained was ground into a fine white powder by forcing it through a small pepper mill.

Cold neutral solutions of collagen were prepared from fresh calf skin. The skin was soaked in a 10 per cent solution of ammonium chloride and 1:1,000 aqueous merthiolate at room temperature for several days. Epidermis, hair, and subcutaneous tissues were loosened by this treatment so that they could be scraped away to produce a clean sheet of tough white dermis. The dermis was coarsely minced with scissors and dialyzed free of salt in the cold room before being extracted with 1,500 cubic centimeters of .5 molar acetic acid with constant stirring for 48 hours. The swollen mass of gelatinous collagen was passed successively through bolting cloth, and through coarse, medium, and fine sintered glass filters until a perfectly clear, highly viscous solution remained. This solution was centrifuged at 15,000 revolutions per minute at 5 degrees C. for 2 hours to insure removal of all tissue fragments. The extract was then dialyzed against 3 changes of cold phosphate buffer—$\mu/2 = .4$, p_H 7.6—until its p_H was 7.2. Such a solution is perfectly clear as long as the temperature remains below 5 degrees C.

Freshly reconstituted collagen fibrils were obtained by either gently adjusting the p_H of the acid extract of rat tail tendon to neutrality with .1 normal sodium hydroxide

or by simply warming a beaker of cold neutral collagen in a water bath set at 37 degrees C. The profuse white flocculent which appeared at the proper *p*H and temperature was dialyzed free of salt to produce pure reconstituted collagen fibrils. After drying by evaporation or lyophilization, the fluffy white fibrils were passed through a pepper mill to produce a fine white powder which can be stored indefinitely.

Wounding procedure and application of collagen preparations. White, female, Sprague-Dawley rats weighing between 165 and 200 grams were used in all of the experiments. After the rats were anesthetized with ether, the hair on the back of their necks and shoulders was clipped, and a 2 centimeter longitudinal incision was made through the skin over the dorsum of the neck midway between the shoulder blades. Wounds in control animals were closed immediately with 4 No. 40 stainless steel wire sutures. Dry collagen preparations were dusted into the wounds as a fine powder or added by simply inserting a piece of lyophilized material between the skin edges. Liquid preparations were introduced with a pipette which was inserted between sutures after the wound had been closed.

No dressing was used and the rates were kept in separate cages. Normal rats were maintained on a diet of purina chow and water ad libitum. Protein-depleted rats were given 15 grams daily of a 4 per cent protein-depletion diet with tap water ad libitum and were pair fed with their control mates. Rats on this regimen lost approximately 20 grams in 7 days.

Testing. Tensile strength in the healing wounds was tested by carefully excising a strip of skin which included a 1 centimeter width of the wound. Subcutaneous tissue was not included and any wounds which appeared infected or which came from rats which appeared ill were discarded. The strip of skin which contained the wound was suspended between clamps according to the method of Charney, Williamson, and Bernhart; and the results were recorded as the number of grams of water which caused a complete dehiscence of the wound. The endpoint was sharp in most instances.

Some of the wounds were extracted with .45 molar saline to determine the rate of collagen production and polymerization. In these experiments, the wounds were excised with a 1 millimeter margin of surrounding skin. The tissue was finely minced with scissors and the wet weight determined. Two volumes of .45 molar saline were added, and the wound tissue was extracted on a mechanical shaker for 24 hours in the cold room. The extract was filtered through coarse, medium, and fine sintered glass filters and was centrifuged at 15,000 revolutions per minute for 2 hours. Viscosity determinations were made at 22 degrees C. in semimicro viscometers with flow times for 20 per cent sucrose of 52 and 47 seconds at that temperature. Microhydroxyproline determinations on the extract were made according to a modification of the Grunbaum technique.

Some of the wounds were sectioned and stained with hematoxylin and eosin for histologic examination.

PROCEDURE

Experiment 1. Two hundred and twenty-four rats were wounded as described in the foregoing. In 56 rats (group I) the wounds were sutured immediately, and the rats were given a normal diet. Fifty-six rats (group II) were fed a protein-depletion diet, and their wounds were also sutured immediately without any supplement being added. Fifty-six rats (group III) were protein-depleted and their wounds were treated by supplementing approximately 5 grams of a powdered acetic acid extract of rat tail collagen. Fifty-six rats (group IV) were protein-depleted and their wounds were dusted with approximately 5 grams of powdered, freshly reconstituted collagen fibrils. The wounds of 8 animals from each group were excised for study at 6, 8, 10, 12, 14, 17, and 21 day intervals.

Experiment 2. This experiment was de-

TABLE I.—TENSILE STRENGTH OF 6 DAY OLD WOUNDS SUPPLEMENTED WITH LYOPHILIZED ACID EXTRACT OF COLLAGEN, ACID COLLAGEN GEL, AND SOLUTION OF COLD NEUTRAL COLLAGEN

No.	*Control*	*Lyophilized acid extract*	*Acid gel*	*Cold neutral solution of collagen*
1	178	295	95	126
2	211	278	90	111
3	125	198	65	119
4	162	268	75	120
5	157	305	100	203
6	191	179	90	129
7	136	205	65	151
8	137	225	75	174
9	138	268		142
10	158	185		182
11	121	252		193
12	185	300		149
13	141	195		214
14	108	165		126
15	209	157		103
16	175	171		253
17	142	172		
18	207	192		
19	162	166		
20	139	155		
21		250		
22		301		
Avg.	159	221*	81†	155

*Significantly greater than control; p<.01.
†Significantly less than control; p<.01.

signed to test the effect of acetic acid extractable collagen, neutral solutions of collagen, and an acid gel of collagen on the wounds of normal animals. The acid gel was nothing more than an extremely viscous solution of collagen in which lyophilized collagen had been made more soluble by soaking it in .5 molar acetic acid before it was inserted into the wound.

Twenty rats were wounded and the wounds resutured immediately to serve as controls. Twenty-two rats received powdered, lyophilized acetic acid-extracted collagen. Eight rats received the acetic acid gel and 16 rats received solutions of cold neutral collagen. All of the wounds in this experiment were excised and tested at 6 days.

TABLE II.—TENSILE STRENGTH (GRAMS OF WATER) OF 3 DAY OLD CONTROL AND ACID EXTRACTABLE COLLAGEN SUPPLEMENTED WOUNDS

Control wounds	*Supplemented wounds*
70	125
60	124
65	144
70	75
75	95
70	179
65	75
70	120
65	106
60	96
62	140
75	70
67	112*

*Significantly >controls; p<.01.

Experiment 3. This experiment was designed to test the effect of acetic acid extracts of collagen on 4 day old secondary wounds. It was hypothesized that the ground substance in a 4 day old wound might be a more receptive substrate for a collagen supplement than the recently exposed tissues of a fresh wound. In this experiment, both normal and protein-depleted animals were tested. Group I consisted of 8 rats on a normal diet which were wounded and 4 days later the wounds were broken open and resutured. These animals served as a control for group II. Group II also consisted of 8 rats on a normal diet which were rewounded 4 days after an initial wound, but these animals received a collagen supplement at the time of the second wound. To serve as a control for group IV, the 8 protein-depleted rats in group III were wounded and rewounded without receiving a collagen supplement. Group IV consisted of 8 protein-depleted rats which received a collagen supplement at the second wounding procedure. All of the wounds in this experiment were tested 3 days after the second wounding procedure.

RESULTS

Experiment 1. The results of the first experiment are shown in Figure 1. Analysis of the curves reveals a highly significant, 1 per cent level, reduction in the rate of gain in tensile strength in the wounds of protein-depleted rats. The data also reveal that in rats which have been fed a 5 per cent casein protein-depletion diet (group II) there is no significant reduction in the strength of their wounds during the precollagen period (0 to 5 days), that ultimately their wounds will become as strong as those of normal animals,

but that the rate of development of wound strength is significantly below that of rats which have been fed a normal diet (group I). The rate of wound healing in rats in which lyophilized acetic acid extract of rat tail collagen was added to their wounds (group III) was not significantly different from that in the pair-fed, protein-depleted controls (group II). The rather marked increase in tensile strength of these wounds at the first, 6 day, observation, however—when in the protein-depleted rat the observed mean was 168, the theoretic mean 167, and in the acetic acid extract treated rat the observed mean was 236, theoretic mean 211—is on the borderline of significance, the probability being 6 per cent on a one-sided test. This is an interesting observation because this is the time when one might expect to see any beneficial effect from the addition of a single dose of a fiber precursor. The significance of this observation is strengthened by the results of Experiment 2, which is a repetition of Experiment 1 except that a larger number of animals on a normal diet were used and there were more control observations.

The wounds which received lyophilized reconstituted collagen fibers (group IV) showed a rate of increase of tensile strength which was not significantly different from the rate of increase in the wounds of their pair-fed, protein-depleted controls. However, the starting point of this curve, or the strength of the wounds at 6 days, was significantly less than the 6 day measurements in other groups. Apparently, the reconstituted collagen fibers acted as a foreign body during the early stages of healing and it seems unlikely from our data that they ever exerted any influence on the wound other than to retard the development of tensile strength.

Experiment 2. The results of Experiment 2 are shown in Table I. Twenty control wounds in normal animals showed an average tensile strength of 159 grams. Although there is not much difference between the tensile strength of wounds from normal and

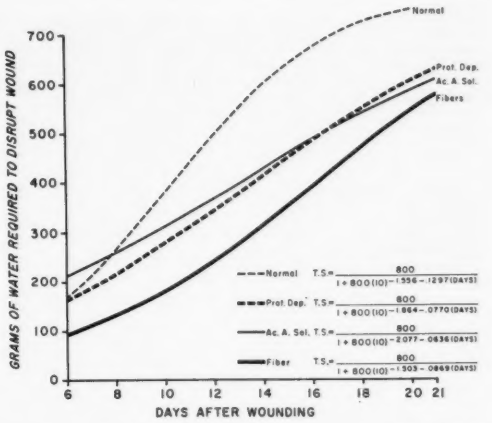

GRAMS OF WATER REQUIRED TO DISRUPT WOUND
DAYS AFTER WOUNDING
Normal
Prot. Dep.
Ac. A. Sol.
Fibers
Normal T.S.= 800 / 1+800(10)^-1.556-.1297(DAYS)
Prot. Dep. T.S.= 800 / 1+800(10)^-1.864-.0770(DAYS)
Ac. A. Sol. T.S.= 800 / 1+800(10)^-2.077-.0636(DAYS)
Fiber T.S.= 800 / 1+800(10)^-1.503-.0869(DAYS)

FIG. 1. Rate of gain in tensile strength of wounds in normal, protein-depleted, and collagen-supplemented rats.

from protein-depleted animals at the 6 day determination, the strength of control wounds in this group was slightly less than that in Experiment 1 because the rats in this experiment were slightly smaller than the rats in Experiment 1.

Wounds supplemented with powdered, lyophilized acetic acid extract of collagen were stronger than their control group by about the same order of significance as the protein-depleted wounds in Experiment 1. A similar effect was also present in 3 day old wounds as shown in Table II. The wounds which were supplemented with cold neutral solutions of collagen did not appear to be affected, either favorably or

TABLE III.—THE EFFECT OF LYOPHILIZED ACID EXTRACT OF COLLAGEN ON TENSILE STRENGTH OF 3 DAY OLD SECONDARY WOUNDS IN NORMAL AND PROTEIN DEPLETED RATS*

	Normal diet		*Protein depleted*	
No.	*Control*	*Collagen supplemented*	*Control*	*Collagen supplemented*
1	278	400	203	504
2	195	169	141	193
3	216	191	139	278
4	282	321	244	200
5	319	444	154	176
6	139	279	259	314
7	226	170	411	180
8	214	228	189	died
Avg.	220	275*	219	263*

Tensile strength, grams of water necessary to disrupt wound.
*Not significantly greater than control.

TABLE IV.—THE EFFECT OF LYOPHILIZED ACID EXTRACT OF COLLAGEN AND RECONSTITUTED COLLAGEN FIBERS ON THE AMOUNT OF SALINE EXTRACTABLE COLLAGEN FROM THE HEALING WOUNDS OF RATS

	3 day wounds			6 day wounds		
No.	*Normal*	*Acid ext. collagen*	*Reconstituted collagen*	*Normal*	*Acid ext. collagen*	*Reconstituted collagen*
1	.960	2.620	.419	1.193	.979	.706
2	.586	.686	.506	1.367	1.668	.694
3	.782	1.525	.300	1.154	1.130	.908
4	1.031	2.775	.989	1.140	2.301	.930
5	1.188	3.150	.856	1.151	2.965	.936
6	1.200	3.651	.499	.936	1.914	.924
Avg.	.957	2.401*	.594†	1.156	1.826‡	.849§

Micrograms of saline extractable hydroxyproline.
*Significantly>normal; p<.02.
†Significantly<normal; p<.01.
‡Not significantly>normal.
§Significantly<normal; p<.015.

TABLE V.—THE EFFECT OF LYOPHILIZED ACID EXTRACT OF COLLAGEN AND RECONSTITUTED COLLAGEN FIBERS ON THE VISCOSITY OF SALINE EXTRACTS FROM HEALING WOUNDS OF RATS

	3 day wounds			6 day wounds		
No.	*Normal*	*Acid ext. collagen*	*Reconstituted collagen*	*Normal*	*Acid ext. collagen*	*Reconstituted collagen*
1	1.13	1.42	1.08	1.18	1.14	1.13
2	1.10	1.14	1.10	1.21	1.26	1.13
3	1.12	1.23	1.08	1.18	1.18	1.16
4	1.16	1.40	1.15	1.15	1.33	1.11
5	1.18	1.51	1.13	1.15	1.49	1.13
6	1.20	1.61	1.08	1.13	1.29	1.12
Avg.	1.14	1.38*	1.10†	1.16	1.28‡	1.13§

Viscosity (centistokes).
*Significantly>normal; p<.02.
†Significantly<normal; p<.01.
‡Not significantly>normal.
§Significantly<normal; p<.015.

unfavorably; the average of their tensile strength at 6 days was almost identical with that of the control observations.

Wounds which were supplemented with an acetic acid collagen gel were adversely affected by the introduction of the acid medium. Healing, as measured by tensile strength, was seriously inhibited, hematomas were frequent, and edema of the wound edges was pronounced. In subsequent experiments, the detrimental action of the acid could be reduced by using a weaker concentration of acid—1 to 10,000 *p*H 3.8; but when the acid was weak enough not to interfere with wound healing, the amount of collagen which it carried was too small to exert any measurable effect.

Experiment 3. The results of adding powdered lyophilized collagen to the surface of 4 day old wounds which had been broken open and resutured after the collagen had been introduced can be seen in Table III. The addition of a soluble collagen precursor appeared to exert a beneficial effect of approximately the same order as in the primary wounds, but the wide variations in tensile strength, which are characteristic of secondary wounds, prevented this effect from being statistically significant in this experiment.

Extraction of the wounds with cold saline revealed that, at 3 days, the amount of tropocollagen available for polymerization in the wounds which were supplemented with acid extractable collagen was over twice as great as that of nonsupplemented wounds and was 4 times as great as that of wounds which were supplemented with freshly reconstituted collagen fibrils (Table IV). At 6 days, wounds treated with acetic acid extract did not reveal a significantly elevated level of tropocollagen, but the wounds which were supplemented with reconstituted fibrils still contained approximately 30 per cent less saline extractable collagen than nonsupplemented wounds. Viscosity determinations on the saline extract from all the wounds revealed that the viscosity of the extract was directly proportional to the hydroxyproline content, or

that the hydroxyproline which was extracted by .45 molar saline was bound in collagen and did not come out as free hydroxyproline (Table V). A more elaborate study on the relationship of viscosity to hydroxyproline content of the saline extract of healing wounds has been completed and this study will be reported upon in another article.

Microscopic examination of the various wounds was most informative in the case of those wounds which were supplemented with reconstituted collagen fibrils (Fig. 2). The insolubility of the added fibrils was obvious and the cellular response which they elicited was tremendous. Large collections of polymorphonuclear granular leukocytes surround the fibers, and in no case were the fibers attached to the dermis. The wounds contained many new fibers, but the fibers apparently did not become incorporated into the new scar tissue at this stage. The tremendous cellular response which the reconstituted fibrils elicited—practically a sterile abscess in some cases—probably accounts for the decreased tensile strength of the wounds. After the first wounds were examined in this series, the experiments were repeated using reconstituted collagen which had been sterilized by ethylene oxide and which was introduced into the wounds under the strictest aseptic conditions. Such measures did not alter the intensity or the type of response to the implant insofar as could be perceived.

The only difference which could be seen between normal wounds and wounds which were supplemented with acetic acid extractable collagen was that, in 8 of 10 supplemented wounds, the subdermal connective tissue appeared thicker and did not separate from the dermis as easily as in normal wounds (Figs. 3 and 4). This observation may be only artifact, but it was independently noted by 2 observers and might possibly indicate a slightly more adhesive or firmer collagenous fixation in the subdermal strata of the supplemented wound. No difference in the cellular response could be noted as regards the relative number or type of cells.

FIG. 2. Photomicrograph of freshly reconstituted collagen fibrils, indicated by arrow, lying unattached in a sterile abscess of a 6 day old wound.

DISCUSSION

Until the various factors which control the polymerization and orientation of newly formed collagen fibrils have been identified and can be measured, tensile strength measurements still have to be utilized to evaluate the total progress of wound healing. There are serious disadvantages of trying to evaluate any single part of the healing complex by a gross measurement such as tensile strength, but, as far as the surgeon is concerned, tensile strength is the ultimate goal of wound healing and any experimental adjuvant to healing will ultimately have to pass the tensile strength test if it is to be of clinical value. That neither cold neutral solution of collagen, acid collagen gel, nor recently reconstituted collagen fibrils was of any value in accelerating the gain of tensile strength in healing wounds of rats is clearly shown by the data in Table I. The acid gel can be quickly dismissed because of the undesirable effects of the acid which was re-

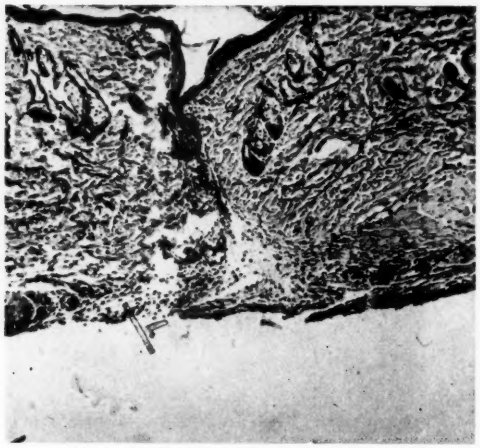


FIG. 3. Photomicrograph of a 6 day old normal wound. Note fragile appearance and depth of subdermal tissue.

quired to dissolve the collagen. The effect of cold neutral solutions of collagen can be discussed simultaneously with the effect of reconstituted fibrils because cold neutral solutions of collagen gelate rapidly to form fibrils within a few minutes after they have been introduced into a warm wound. The concentration of the collagen fibrils in these solutions, once they have been reconstituted, was much less than that of lyophilized fibers; thus the difference between the solution which caused no effect on the tensile strength and the concentrated lyophilized fibrils which inhibited healing as shown in Table I is probably only a difference in concentration of the supplements.

The reason for the reduction of tensile strength in the fibril supplemented wounds is apparent in the photomicrographs. These results also point out that having increased amounts of collagen in a wound is not enough to insure optimal gain in tensile strength. The collagen must be purposely woven into patterns which are strong and will bind the wound edges together. The difference between a wound full of artificially reconstituted collagen fibrils and a wound in which the new collagen is polymerizing slowly along predirected patterns is somewhat analogous to the difference between a quantity of raw cotton and a cotton dress; the amount of cotton in each may be the same, but the functional results of organization are vastly different. Thus, the total collagen content of a wound can be misleading insofar as progress in healing is concerned unless it is also known that the newly formed collagen is polymerizing in structurally desirable patterns.

The beneficial effect on the development of tensile strength in wounds which received the lyophilized acid extract of collagen is much more difficult to explain. The effect was constant in both primary and secondary wounds, in depleted and in normal animals. Moreover, the effect was maximum at the 6 day determination, which is what might have been predicted from a 1 dose administration of a supplement which would exert its effect from the moment of introduction until it was completely consumed. Three days after wounding there is also a statistically significant beneficial effect from adding lyophilized acetic acid extracts of collagen, as shown in Table II.

The most important question which needs to be answered in order to interpret the data is whether the increase of tensile strength in the collagen supplemented wounds was due to a nonspecific irritating effect or whether the collagen precursors were actually reconstituted into fibrils which, since they were polymerized slowly by the ground substance, were incorporated into the new scar tissue. The saline extract analyses revealed that at 3 days there was a significant increase in the amount of tropocollagen which was available to the wounds which had been supplemented with a lyophilized extract of collagen. That this tropocollagen came from the supplement is suggested by the fact that 1 hour after introduction of the supplement, the saline extract from the wound is so viscous that it gels in the viscometer. Saline extractable or monomeric collagen which can be measured as such on the third day would be converted to insoluble polymerized collagen by the sixth day. Tensile strength determinations,

therefore, lag 2 or 3 days behind tropocollagen determinations, if the two are related as they appear to be. In our experiments, tropocollagen levels are not significantly different in collagen supplemented and normal wounds on the sixth day. By the eighth day, the maximal effect on tensile strength from the supplement is over, and both treated and untreated wounds appear equally strong for the rest of the healing period.

The most disappointing part of the experiment was the failure to influence favorably the strength of wounds any more than approximately 50 grams at 6 days. If too little collagen was added, there was no effect, and if too much was added, a foreign body effect similar to that which was seen after the addition of reconstituted fibers resulted and the wound strength was decreased. The reaction to collagen supplements appears to be an all or nothing at all phenomenon, and it was not possible to increase it by changing either the amount of collagen or the time in which it was introduced (Experiment 3). Although an average increase of 50 grams is interesting and is mathematically significant, an increase of no more than 50 grams in a 6 day old wound is hardly clinically significant. Because of the rapidity of the reconstitution phenomenon during heat gelation and after *p*H adjustment, we know that collagen fibers can be produced rapidly when the building blocks are present in sufficient strength and when the conditions in the surrounding media are optimal. The orientation of collagen fibers into strong structural patterns is another matter, however, and the forces which control orientation are virtually unknown. It is possible that the ground substance is involved by acting as a template or latticework for new collagen fibers to be polymerized on. Acetic acid extract of collagen added to 4 day old wounds to explore this possibility, however, did not increase the tensile strength any more than when it was added to fresh wounds. These results suggest, therefore, that the problem is not simply one of adding the collagen at the correct time.

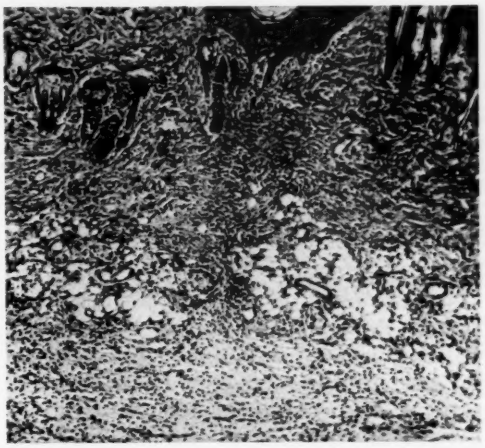


FIG. 4. Same power photomicrograph as Figure 3 of a 6 day old healing wound which was supplemented with acetic acid-extractable collagen. Note the thickness and edema of subdermal tissue.

Although the evidence is not conclusive, it seems most logical to assume that the small increase in tensile strength observed following the addition of acid extract of collagen is probably only due to a nonspecific irritating or inflammatory phenomenon which causes an increased cellular activity. The constancy of this type of reaction, in spite of variation in dose and time of administration, has also been seen after the addition of other substances. Microscopic examination strongly suggests, however, that the irritative or inflammatory response is probably due to an accelerated activity by individual cells rather than to a marked increase in the number of cells.

The pronounced cellular reaction following the administration of reconstituted fibrils is quite different from the response to acid extracts in that this amount of cellular response is obviously detrimental to the over-all healing process. In this regard, it should be noted that reconstituted collagen is occasionally suggested as a dressing and suture material for clinical use. Such materials frequently are called biologic dressings or sutures, a term which suggests that the collagen enters into the healing process. The results of our experiments show that once

the fibrils have been reconstituted they are no different from any other long chain, high-molecular weight polymer and that there is no evidence that they ever become part of the recipient animal's collagen system. If collagen from an external source has any chance to participate in the formation of new scar tissue, it would seem that it will probably have to be introduced as a monomeric or prepolymerized form so that the complex forces in the ground substance can control the polymerization and orientation of the new fibrils. That the monomeric collagen which appeared of some benefit in our experiments acted in this matter is entirely conjectural. Relatively meteoric developments in the understanding and control of collagen synthesis in vitro and in vivo, however, strongly suggest that eventual acceleration and control of the healing process will be possible to a degree which will not only be mathematically significant but clinically significant as well.

SUMMARY AND CONCLUSIONS

1. By using the heat gelation of cold neutral solutions of collagen as a laboratory model for the production of collagen fibrils in healing wounds, the effect of acid extracts of collagen, cold neutral solutions of collagen, and freshly reconstituted collagen fibrils have been investigated in the healing wounds of rats.

2. The effect of the various collagens has been measured by evaluation of tensile strength of the wounds, measuring the amount of saline extractable collagen in the wounds, and histologic examination of the tissues.

3. Acetic acid extracts of collagen exerted a significant, although limited, beneficial effect on the healing process. Reconstituted collagen fibrils significantly retarded the healing process.

4. The mechanisms by which the various collagen preparations influenced healing have been hypothesized on the basis of the saline extraction and histologic studies.

REFERENCES

1. Charney, J., Williamson, M. B., and Bernhart, F. W. An apparatus for the determination of the tensile strength of healing wounds. Science, 1947, 105: 396.
2. Gross, J., Highberger, J. H., and Schmitt, F. O. Extraction of collagen from connective tissue by neutral salt solutions. Proc. Nat. Acad. Sc., U. S., 1955, 41: 1.
3. Gross, J., and Kirk, D. The heat precipitation of collagen from neutral salt solutions; some regulating factors. J. Biol. Chem., 1958, 233: 355.
4. Grunbaum, B. W., and Glick, D. Studies in histochemistry; XLV, determination of hydroxyproline in microgram amounts of tissue. Arch. Biochem., 1956, 65: 260.
5. Orekhovitch, V. N., and Shpikiter, V. O. Procollagens as biological precursors of collagen and the physio-chemical nature of these proteins. Council for International Organizations of Medical Science, Symposium on Connective Tissue. P. 281. London: Blackwell Publications Ltd., 1947.
6. Peacock, E. E. Effect of dietary proline and hydroxyproline on tensile strength of healing wounds. Proc. Soc. Exp. Biol., N. Y., 1960, 105: 380.

SUPERFICIAL CARCINOMA OF THE UTERINE CERVIX IN PREGNANCY

J. G. MOORE, M.D., D. G. MORTON, M.D., J. W. APPLEGATE, M.D., and R. A. BASHORE, M.D., Los Angeles, California

EARLY CANCER of the uterine cervix presents special problems during pregnancy. Authorities across the country differ in their opinions concerning the diagnostic features, clinical significance, and management of early cervical cancer during pregnancy. In the past, some have doubted that intraepithelial carcinoma could be distinguished from the less significant epithelial atypias associated with pregnancy. The clinical significance of epithelial changes during pregnancy is variously interpreted. Greene and Peckham have presented evidence, and we agree, that intraepithelial carcinoma can be diagnosed with confidence during pregnancy. Schmitz and associates advocate cytologic screening of all prenatal patients, whereas Birtch and Beecham and their coworkers believe that this procedure is not necessary unless there is a clinically suspicious lesion found on physical examination. Many gynecologists are reluctant to employ an adequate diagnostic conization during pregnancy. Because of these differences, there has been a wide variation in the management of early cancer in pregnancy. Our experience during the past decade has served to crystallize our ideas regarding these problems and has led us to formulate certain features in the management of early cervical lesions during pregnancy.

It is now generally accepted that multiple punch biopsies are not adequate for a complete evaluation of early restricted cervical cancer. Although it may be regarded as somewhat more difficult and dangerous in the pregnant patient, cold knife conization, as a hospital procedure with adequate study of the specimen, would appear to give the most pertinent information without provoking undue complication. In addition, the conization procedure will often serve as definitive therapy.

In our group of 14 pregnant patients, lesions in 12 were detected by vaginal cytology alone. The other 2 had, in addition to positive cytologic findings, nonspecific circumoral erosions associated with vaginal spotting. In these 2 cases, punch biopsies were taken from Schiller positive areas, and intraepithelial carcinoma was diagnosed. All of the patients were then subjected to a cold knife conization of the cervix. As a result of the conization survey the patients were found to have either a suspicious epithelial atypism, intraepithelial carcinoma (Figs. 1 and 2), microinvasive carcinoma (Fig. 3), or, in 1, infiltrative carcinoma.

Since 1954 for purposes of therapy we have classified cases of squamous cervical cancer with questionable superficial stromal invasion as stage 0. A fully evaluated specimen by cervical conization is necessary in order to qualify the lesion for stage 0 classification. The lesion must be confined to the surface epithelium or cervical glands or, if it is present, stromal invasion must be restricted to the 2 to 3 millimeters of stroma immediately subjacent to the surface epithelium. If the pattern of the lesion is frankly infiltrative even though definitely restricted, or if a superficial lymphatic is seen to be involved, the lesion is not classified as stage 0.

We have treated the nongravid patient with stage 0 cancer by nonradical methods

From the Department of Obstetrics and Gynecology, University of California School of Medicine, Los Angeles.

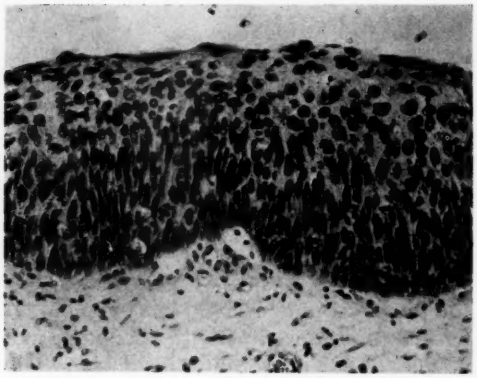


FIG. 1.

FIG. 1. Intraepithelial carcinoma involving surface epithelium. ×157.

FIG. 2. Intraepithelial carcinoma showing involvement of cervical gland. ×101.

FIG. 2.

(7). They have been either carefully followed up after conization, subjected to restricted irradiation, or treated by a simple total extrafascial hysterectomy. When this diagnosis was established by conization during pregnancy, these patients were allowed to carry their pregnancies to term and to deliver vaginally. After delivery they were followed up carefully with vaginal cytology or subjected to total abdominal hysterectomy.

The patients with suspicious epithelial atypias have been sufficiently treated by the conization and present little further problem in management. Since the malignant potentialities of the untreated atypia have been documented by McKay and associates, it is important that these patients be submitted to careful follow up. The patient with the frankly infiltrative cancer presents little leeway in management and should be subjected to the full therapy that this disease requires.

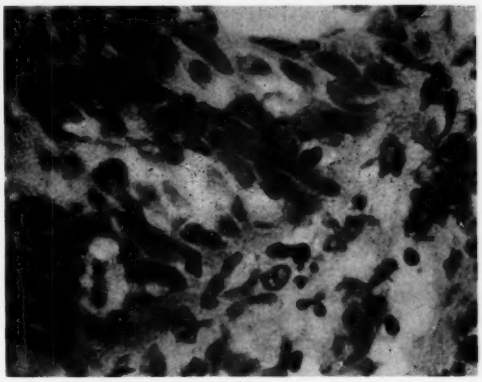
The purpose in this study is to review the experience with cervical conization in pregnancy, emphasizing the management, the complications encountered, and the short term results of therapy. Of special interest is the effect of conization on pregnancy and subsequent delivery.

MATERIAL AND METHODS

Twelve patients were subjected to conization in the investigation of early cervical cancer during pregnancy. In 2 additional patients with cancer detected during late pregnancy, conization was carried out in the immediate postpartum period and both were then observed during subsequent pregnancies and deliveries. These 14 pregnant patients were taken from a series of 285 having conizations carried out on the obstetric and gynecologic services of the University of California Medical Center Los Angeles, Los Angeles County, Harbor General, and City of Hope Hospitals. These patients were studied by cervical conization in the investigation of cervical cancer from 1950 to 1960.

After positive or repeated suspicious vaginal cytologic findings or after a punch

a



b

FIG. 3. a, Intraepithelial carcinoma involving surface epithelium and cervical glands with possible microinvasion. ×65. b, High power view indicating area of microinvasion. ×220.

biopsy indicating intraepithelial carcinoma, the patients were subjected to cervical conization. The conization was carried out with a No. 11 Bard-Parker scalpel blade, and an attempt was made to remove a specimen measuring 2 centimeters in diameter across the vaginal portio and 1 to 2 centimeters in depth, depending on the amount of cervical effacement. Care had to be taken to stay below the internal os and to avoid rupturing the membranes. It was considered helpful to use hemostatic sutures placed in the lateral substance of the cervix high up in the lateral fornices. Used as guy wires these sutures were also very helpful in maintaining exposure. The cone site was usually left open, but in some instances the vaginal portio of the cervix was covered with an epithelial flap to maintain hemostasis. So far in this series, hemorrhage has not been a problem during the procedure or in the postoperative period. No patients required transfusions, although 1 patient bled 350 cubic centimeters during the first 24 postoperative hours.

The specimens were then serially blocked into at least 12 to 14 portions. Care was exercised to orient the block surfaces properly during the embedding procedure in order that some evaluation of clearance of the lesion might be assessed. Step sections were made throughout each block and reviewed. Additional sections were taken, depending upon the diagnostic problem involved.

Patients ranged in age from 21 to 36 years, average, 27 years. Number of pregnancies ranged from 1 to 8, average 4, and the average parity was 3. At the time of conization the duration of pregnancy ranged from 2½ to 6 months, average 4 months. It is interesting to note that the oldest patient in this group was an elderly primipara and was the only patient found to have infiltrative carcinoma.

The tissue diagnosis based on conization specimens from these 14 pregnant patients was: infiltrative carcinoma in 1 case, 7 per cent; carcinoma with microscopic invasion in 4 cases, 29 per cent; intraepithelial car-

TABLE I.—CLINICAL COURSE OF PATIENTS CONED DURING PREGNANCY OR IMMEDIATE POSTPARTUM PERIOD

Pt. Age, yrs.	Gravida and para	Duration of pregnancy at time of conization	Size of cone, cms.	Histologic diagnosis	Clearance of lesion demonstrated	Definitive therapy	Residual cancer found	Duration of pregnancy at delivery, wks.	Length of labor	Infant weight, grams	Comments
1 21	3 2	5 months	1.5x1.5	Epithelial atypism	—	Conization alone	—	41	2 hr. 53 min.	3420	Uneventful labor and delivery
2 28	8 5	5 months	1.0x1.0	Intra-epithelial carcinoma	No	Radical hysterectomy	Yes				Radical hysterectomy and pelvic lymphadenectomy during pregnancy
3 32	6 5	3 months	3.2x1.0	Micro-invasive carcinoma	No	Conization alone	—	40	8 hr.	3100	One year later delivered 5 lb. 15 oz. infant at 38 weeks after 11 hrs. labor. No complications. Now 7 mos. pregnant. Pap. smear negative
4 24	7 5	4½ months	2.5x0.5	Micro-invasive carcinoma	No	Total hysterectomy after delivery	No	40	5 hr. 36 min.	3000	Uneventful labor and delivery
5 30	4 2	3 months	4.5x1.5	Micro-invasive carcinoma	No	Total hysterectomy after delivery	Yes	40	5 hr. 3 min.	3660	Uneventful labor and delivery
6 23	7 5	4½ months	1.5x1.0	Intra-epithelial carcinoma	Yes	Total hysterectomy after delivery	No	40	8 hr. 20 min.	2880	Cervical laceration at delivery; subsequent pregnancy ended prematurely, 1900 gm. infant
7 27	2 1	5½ months	2.5x1.0	Micro-invasive carcinoma	Yes	Total hysterectomy after delivery	No	40	6 hr. 30 min.	3570	Uneventful labor and delivery
8 36	1 0	2½ months	2.0x2.0	Infiltrative carcinoma	No	Radical hysterectomy	No				Radical hysterectomy and pelvic lymphadenectomy during pregnancy
9 26	2 1	4 months	2.5x1.5	Epithelial atypism	—	Conization alone	—	41	7 hr. 13 min.	4500	Uneventful labor and delivery
10 32	6 5	4 months*	3.0x2.0	Intra-epithelial carcinoma	No	Conization alone	—	41	28 hr. 38 min.	3780	Oxytocin induction, 24 hrs. first st., persistent OP, prolonged 2nd st.
11 24	4 2	6 months	1.5x1.5	Intra-epithelial carcinoma	Yes	Conization alone	—	40	6 hr. 33 min.	3750	Subsequent delivery uncomplicated 14 hrs. 10 mins. labor, 3800 gm. infant
12 27	5 4	5 months	5.0x2.0	Epithelial atypism	—	Conization alone	—		Delivered elsewhere		Lost to follow-up
13 28	2 2	6 weeks postpartum	2.5x2.0	Intra-epithelial carcinoma	Yes	Conization alone	—	35	7 hr. 19 min.	2409	Premature rupture of the membranes
14 21	4 4	12 weeks postpartum	1.5x1.5	Epithelial atypism	—	Conization alone	—	38	2 hr. 50 min.	3480	Subsequent delivery uncomplicated; 6 hrs. 28 mins. labor, 4110 gm. infant

*350 cubic centimeter blood loss during first 24 postoperative hours.

cinoma in 5 cases, 35 per cent; and nonmalignant epithelial atypia in 4 cases, 29 per cent. The pathologic tissue diagnosis based on conization specimens from 271 nongravid patients was: infiltrative carcinoma in 27 cases, 10 per cent; carcinoma with microscopic invasion in 64 cases, 24 per cent; intraepithelial carcinoma in 83 cases, 30 per cent; and nonmalignant epithelial atypia in 97 cases, 36 per cent. It is of special note that the distribution of pathologic diagnoses in this group of pregnant patients shows no significant deviation from the findings in the large group of nonpregnant patients.

One might infer from this correlation that vaginal cytology or a punch biopsy showing intraepithelial carcinoma has the same significance in the pregnant patient as in the nonpregnant. This inference does not necessarily mean that the neoplasm carries the same prognostic significance as to eventual outcome but it does suggest that the geographic extent of the lesion is not affected by pregnancy.

After conization, 1 patient with a stage 1 lesion had a radical hysterectomy and pelvic lymphadenectomy at 2½ months gestation; 1 with stage 0 cancer had a radical hysterectomy and pelvic lymphadenectomy at 5 months gestation; 4 had total hysterectomy at 6 to 12 weeks postpartum; 4 had follow-up study only; and 4 with nonmalignant epithelial atypia had follow-up only.

These data suggest that our management has varied over the last 10 years. Two patients were subjected to radical hysterectomy and pelvic lymphadenectomy. One was operated upon for early infiltrative carcinoma and the other, at an early phase in the series, was radically operated upon for what we would now diagnose as a superficial microinvasive carcinoma. The remaining 10 patients were allowed to continue their pregnancies to term and to deliver vaginally. Four of these patients had total abdominal hysterectomy 6 to 12 weeks postpartum and 4 had no further treatment than the conization. Logically, the patients with nonmalignant squamous atypia were not subjected to hysterectomy after delivery.

Of the 10 patients with cancer, 4 were assessed as cleared by the cone and 6 could not be so designated. It should be stated that when the clearance was doubtful, it was classified as not cleared. This explains the patients judged not cleared in which no residual lesion was found. Of the 4 patients judged cleared, no evidence of residual tumor was found, whereas, in the group of 6 not cleared patients, 2 had residual tumor in the hysterectomy specimen. It is particularly distressing that a positive vaginal cytologic finding was obtained at the last clinic visit of 1 of these patients.

Fifteen vaginal deliveries subsequent to conization were observed in this group of patients. Three patients experienced precipitous labors, lasting from 0 to 4 hours. One patient had a very difficult labor after oxytocin induction 1 week beyond term. Labor had been induced because of a history of precipitous labor and long transportation time from the home to the hospital. This patient's fetus was in a persistent occipitoposterior position and there were a prolonged second stage, difficult forceps rotation, and shoulder dystocia at delivery. Another patient at delivery had an extensive cervical laceration which required repair. This patient's next pregnancy ended with delivery of a 1,900 gram premature infant after spontaneous premature rupture of the membranes. The only other premature delivery in this group was also associated with premature rupture of the membranes.

DISCUSSION

Routine vaginal cytology in the nonpregnant patient is now established as an excellent screening device to uncover unsuspected early cervical cancer. Our experience indicates that its role in the pregnant patient is of equal significance. The lesions of 12 of the 14 pregnant patients studied might not have been detected without vaginal cytology. One of these patients had an early

infiltrative carcinoma which was not suspected on physical examination. In view of the fact that many patients in this age group seek medical attention only during pregnancy, routine prenatal vaginal cytology provides an excellent screening device. Johnson has emphasized very effectively the important role of the obstetrician in this screening service.

After suspicious vaginal cytology or a punch biopsy indicating intraepithelial carcinoma, cold knife conization seems indicated in the pregnant patient. This review again indicates that cervical conization is the best method of excluding an area of infiltrative cervical cancer associated with intraepithelial carcinoma. Punch biopsies showing intraepithelial carcinoma are considered inadequate in our hands for the evaluation of the lesion in pregnant as well as in nongravid patients.

The distribution of pathologic diagnoses on conization was found to be essentially the same in the pregnant group as in the nonpregnant series. This correlation indicates that pregnancy per se probably has little effect on the geographic extent of the lesion at the time that these subclinical lesions are detected with the aid of vaginal cytology.

Once the diagnosis has been established by cervical conization, the method of definitive therapy must be determined. We believe that the patients with superficial microinvasive carcinoma should be placed in the stage 0 group. These patients are allowed to carry the pregnancy to term, deliver vaginally, and may be treated by total abdominal hysterectomy after delivery. Just as in the nonpregnant patient, cancerocidal irradiation or radical hysterectomy and pelvic lamphadenectomy with the attendant morbidity does not seem justified for this superficial lesion when microinvasion is delimited. It must be stated, however, that if the histologic pattern is that of infiltrative carcinoma, even though restricted, or if lymphatic channels are involved in the superficial stroma, the lesion is regarded as stage 1 and treated with full cancerocidal irradiation or radical surgery.

In our experience, conization of the cervix during pregnancy had virtually no immediate effect on the pregnancy. Table I outlines the experience in each case. Postoperative bleeding proved to be no more of a problem in the pregnant patient than in the nonpregnant patient. No abortions followed the conization. Late complications possibly related to the procedure included 1 cervical laceration at delivery, and 2 premature ruptures of the membranes followed by premature labor and delivery. Although these patients were not examined just prior to the rupture, it is possible that the premature rupture of membranes was due to cervical incompetence. These complications were not of serious significance in our series and indeed may not have been related to the conization.

It should be recognized that this series is small and that with a larger experience one might expect a greater number of complications. Ferguson reported 50 conizations during pregnancy. In 8 of his cases, the pregnancy failed to produce a surviving baby, although by correction of the data on fetal loss only 3 of the fetal deaths were attributed to the conization. One must strike a compromise in depth of the conization in the pregnant patient to avoid some of the immediate complications. However, in light of the disease uncovered by the procedure, cervical conization would seem worthwhile and safe when indicated in pregnancy.

SUMMARY

1. Twelve pregnant patients suspected of subclinical cervical cancer were subjected to conization of the cervix during pregnancy.

2. Fifteen pregnancies and vaginal deliveries were observed subsequent to the cervical conization.

3. Tissue diagnoses based on the conization specimens included 1 infiltrative carcinoma, 4 superficial microinvasive carcinomas, 5 intraepithelial carcinomas, and 4 nonmalignant epithelial atypias.

4. The distribution of pathologic diagnoses made by conization of the pregnant patients showed a marked similarity to the distribution of pathologic diagnoses in the series of nongravid patients. This similarity would seem to indicate that pregnancy per se does not affect the geographic distribution of the lesions at this early stage of the disease.

5. For purposes of management, the superficial microinvasive lesions were grouped with the truly intraepithelial cancers as stage 0.

6. Immediate and late complications of conization of the cervix during pregnancy were not significant.

7. Conization of the cervix is as valuable a diagnostic procedure in evaluating the extent of early subclinical cervical cancer in the pregnant patient as in the nongravid patient.

REFERENCES

1. BEECHAM, C. T., and ANDROS, G. J. Cervical conization during pregnancy. Obst. Gyn., 1960, 16: 521–526.
2. BIRTCH, P. K., and RANDALL, C. L. Pregnancy relationships to carcinoma in situ. N. York J. M., 1959, 59: 3783–3788.
3. FERGUSON, J. H., and BROWN, G. C. Cervical conization during pregnancy. Surg. Gyn. Obst., 1960, 111: 603–606.
4. GREENE, R. R., and PECKHAM, B. M. Preinvasive cancer of cervix and pregnancy. Am. J. Obst. Gyn., 1958, 75: 551–564.
5. JOHNSON, L. D. The role of the obstetrician in the prevention of cervical cancer. N. England J. M., 1960, 262: 1297–1301.
6. MCKAY, D. G., TERJANIAN, B., POSCHYACHINDA, D., YOUNG, P. A., and HERTIG, A. T. Clinical and pathological significance of anaplasia (atypical hyperplasia) of the cervix uteri. Obst. Gyn., 1959, 13: 2–21.
7. MOORE, J. G., MORTON, D. G., APPLEGATE, J. W., and HINDLE, W. The management of early carcinoma of the uterine cervix. Am. J. Obst. Gyn., 1961, 81: 1175-1182.
8. MORTON, D. G. Carcinoma in situ of the uterine cervix. Clin. Obst. Gyn., 1958, 1: 1003–1012.
9. SCHMITZ, H. E., ISAACS, J. H., and FEATHERSTON, W. C. A report upon the value of routine cytologic smears in pregnancy. Am. J. Obst. Gyn., 1960, 79: 910–913.

ARTERIOGRAPHIC FINDINGS IN CONGENITAL ABNORMALITIES OF THE MESENTERY AND INTESTINES

FIDELIO A. JIMENEZ, M.D., and LEOPOLD REINER M.D., New York, New York

DESPITE an abundant literature on the subject of congenital malformations of the intestinal tract, little or no attention has been paid to any associated vascular patterns. This article is presented to describe some observations on the mesenteric arterial vasculature as identified by postmortem arteriography in a small number of cases of congenital abnormalities of the intestine and mesentery.

MATERIALS AND METHODS

The abdominal viscera of 16 neonates and children were studied by postmortem arteriography. Congenital abnormalities of one type or another were identified in 11 (Table I). In 6 of the 11 cases there were abnormalities of the mesentery together with intestinal malrotation. It is these 6 instances that constitute the subject of the current report with the remaining 10 of the series serving as controls. Among the 6 there were: 1 with duodenojejunal atresia, 2 with diaphragmatic hernia, and 1 with heterotaxia of the abdominal viscera and agenesis of the spleen.

The technique of study has been described previously (13). In short, it comprises: en bloc removal of the abdominal viscera; cannulation of the aortic ostia of the celiac, superior mesenteric and inferior mesenteric arteries; injection of these arteries with a radiopaque mass of barium sulfate in a gelatine menstruum; partitioning of the abdominal viscera in accordance with the arborizations of the three constituent arteries; upward rotation of the head of the pancreas and duodenum; and the preparation of stereoscopic arteriograms. For purposes of comparison with the subsequent cases a standard diagram of the celiac arborization and the root of the superior mesenteric artery is depicted in Figure 1.

Such terms as "mesenteric arteries" and "mesenteric circulation" are used in the following text to denote the vasculature of the entire gastrointestinal tract and thus include the superior and inferior mesenteric arteries proper as well as the celiac axis.

MATERIAL

CASE 1. A full term male infant was operated upon for a right diaphragmatic hernia 18 hours after delivery. The surgeon reported that the distal portion of the duodenum, together with the entire small and large intestines including the sigmoid, was displaced into the right side of the chest cavity, as was the right lobe of the liver. A large portion of the right hemidiaphragm was missing, and not enough tissue was available for complete surgical repair. The baby expired within hours after completion of the operation.

Autopsy findings. The large bowel was redundant and presented a large mesocolon particularly in its descending and sigmoidal portions. The liver showed a deep vertical groove, an imprint of the left hemidiaphragm. The mediastinum was shifted toward the left. The right pleural space was reduced by the herniated ipsilateral kidney and adrenal which were intimately fused to the hypoplastic right lung and which in turn was fused to the right lobe of the liver.

Angiography. There was no celiac axis. Instead, its constituent units, i.e., the left gastric, splenic, and gastrohepatic arteries, arose by independent, though closely adjacent ostia from the aorta whence they followed their normal course. There were atypias, not fully evaluated, in relation to the pancreaticoduodenal arcades and the dorsal pancreatic artery.

A separate origin from the aorta of each of the three constituent arteries which normally arise from a common celiac axis is an exceedingly rare anomaly. From the series

From the Department of Laboratories, The Bronx Hospital and the Department of Pathology, Albert Einstein College of Medicine, New York.

This work was supported by Research Grant H-2542 (C4) of the National Heart Institute, National Institutes of Health, Public Health Service.

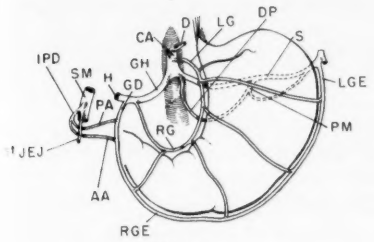


FIG. 1.

FIG. 1. Standard diagram of the celiac arborization and of the root of the superior mesenteric artery. The drawing is based upon the roentgenographic appearance following partitioning of the abdominal viscera and combined upward rotation of the duodenum and head of the pancreas. For this reason, the superior mesenteric is to the right of the celiac axis rather than below it; and the pancreaticoduodenal arcades describe an upward rather than a downward curve. In accordance with our experience, the inferior pancreaticoduodenal artery joins the first jejunal rather than the main stem of the superior mesenteric artery.

Labeling for all illustrations: *AA*, anterior pancreaticoduodenal arcade; AMC, accessory middle colic; *CA*, celiac axis; *D*, diaphragmatic; *DP*, dorsal pancreatic; *GD*, gastroduodenalis; *GH*, gastrohepatic; *H*, hepatic; *1st JEJ*, first jejunal; *IPD*, inferior pancreaticoduodenalis; *LG*, left gastric; *LGE*, left gastroepiploic; *PA*, posterior pancreaticoduodenal arcade; *PM*, pancreatica magna; *RG*, right gastric; *RGE*, right gastroepiploic; *S*, splenic; *SM*, superior mesenteric.

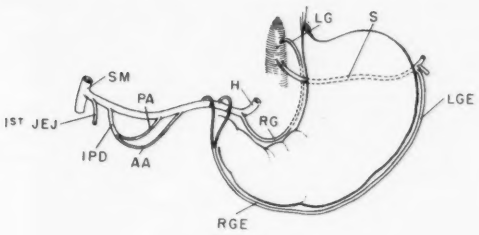


FIG. 2.

FIG. 2. Case 2. Diagram of celiac arborization and root of superior mesenteric artery. For explanation, see text.

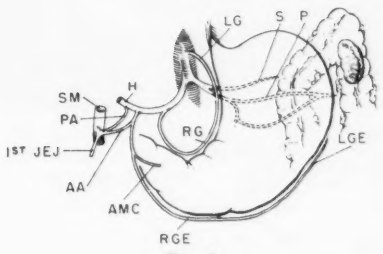


FIG. 3.

FIG. 3. Case 4. Diagram of celiac arborization and root of superior mesenteric artery. For explanation, see text. Note the atypical origin of the posterior pancreatic arcade from the hepatic instead of from the gastroduodenalis.

of 596 cases collected by Eaton, we infer that this anomaly was encountered in 3, 0.5 per cent. This vascular pattern recalls a very early stage of embryonal development, since according to Pernkopf a common celiac axis can be recognized as early as the 5 millimeter stage. Earlier still, the left gastric, splenic, and gastrohepatic arteries arise independently from the aorta being connected to each other by a preaortic longitudinal anastomosis as worked out by Tandler. Incomplete formation of this anastomosis or faulty interruption following its formation would explain the vascular arrangement observed in the present case.

CASE 2. The case was of a full term, stillborn female anencephalic monster with complete craniospinal rachischisis.

Autopsy findings. The bulk of the small intestine was situated to the left of the midline, whereas the entire large intestine was confined to the right half of the peritoneal cavity. The cecum was located just to the right of the midline near the umbilicus. On reaching the liver, the colon looped first to the right and then back to the left as a transverse redundant loop which continued into a normally situated descending colon. The mesentery and mesocolon presented numerous anomalies which were not completely resolved. Among these was a freely movable and completely peritonealized duodenum.

Angiography (Fig. 2). There was no celiac axis. The splenic and the left gastric arteries arose by independent ostia from the aorta, whereas the hepatic took origin from the superior mesenteric. The hepatic artery gave off the following branches: (a) the first jejunal artery, (b) the inferior pancreaticoduodenalis, (c) the right gastroepiploic which was atypically formed by the fusion of two equal-sized arteries arising by independent ostia, and (d) the right gastric. The superior mesenteric artery itself showed a normal pattern.

In the actual arteriogram the two roots of the right gastroepiploic arose opposite rather than distal to the two pancreatic arcades. The distortion in the diagram was made for reasons of pictorial clarity.

This case was an example of hepatomesenteric trunk. However, the bipodal

TABLE I.—CONGENITAL ANOMALIES IN 16 CASES STUDIED BY POSTMORTEM MESENTERIC ARTERIOGRAPHY

Case	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*
Sex	*M*	*M*	*F*	*M*	*M*	*M*	*M*	*M*	*F*	*M*	*M*	*F*	*M*	*M*	*M*	*F*
Age[1]	*1d*	*2d*	*SB*	*6y*	*3h*	*1w*	*1h*	*10d*	*1h*	*3w*	*SB*	*1m*	*SB*	*1h*	*8m*	*3h*
Prematurity		+				+	+	+	+					+		+
Abdominal cavity																
Abnormalities of mesentery[2]	+	+	+	+	+	+										
Intestinal malrotation	+[3]	+	+	+	+[3]	+										
Duodenojejunal atresia						+										
Aplasia of spleen				+												
Omphalocele					+											
Anomalies of extrahepatic biliary system			+						+							
Megacolon								+								
Atresia ani									+							
Genitourinary tract																
Hydroureter and hydronephrosis		+	+	+										+		
Megalourovesicle		+	+	+										+		
Polycystic kidneys									+							
Cryptorchidism		+		+	+											
Musculoskeletal system																
Hypoplasia of abdominal muscles			+	+												
Diaphragmatic hernia	+				+											
Clubbing of extremities		+	+						+							
Polydactylia					+											
Central nervous system																
Anencephalus			+											+		
Hydrocephalus												+				
Spina bifida			+	+												
Miscellaneous																
Double aortic arch										+						
Hermaphroditism									+							
Hypoplasia of lung	+				+				+							

The first 6 cases constitute the subject of this report. Cases 7 to 16 are the control group.
[1]h—hours; d—days; w—weeks; m—months; y—years; SB—Stillborn.
[2]Including anomalies of the mesocolon.
[3]Associated with diaphragmatic hernia.

gastrosplenic trunk which is usually associated with a hepatomesenteric trunk did not exist. Instead, the left gastric and splenic arteries arose by independent ostia from the aorta. We were unable to find a duplicate of this combined vascular constellation in the literature. However, as an isolated phenomenon, an independent origin of the splenic artery from the aorta was observed by Lipschutz in 7.2 per cent of 83 anatomic dissections and not at all by Adachi in 252 (Japanese) bodies. Also as an isolated phenomenon, an aortic origin of the left gastric artery occurred in less than 3.5 per cent of 200 unselected adults who were studied by Michels; it was usually associated with a bipodal axis composed of the hepatic and splenic arteries—the hepatolineal trunk.

This case resembled Case 1 in that there was no celiac axis, but differed from it in that the hepatic artery did not arise from the aorta.

CASE 3. The case was of a premature male infant weighing 2,300 grams and cyanotic since birth. The baby died on the second postpartum day.

Autopsy findings. The abdomen was tremendously dilated, imparting to the baby a batrachian appearance. The abdominal wall was paper-thin both from overstretching and from hypoplasia of the anterior abdominal wall musculature. The capacity of the abdominal cavity was in excess of what seemed needed for the viscera. The cecum was lodged high in the concavity of the duodenum. Just above the cecum, the ascending colon showed a small perforation secondary to transmural infarct necrosis of uncertain cause. The perforation was partly sealed off by fibrinous exudate. Focal fibrinous peritonitis with dilatation of several loops of small intestine was also encountered. There was 60 cubic centimeters of dirty-gray fluid admixed with meconium in the peritoneal cavity. There was bilateral hydronephrosis and hydroureter.

Angiography. The celiac axis was reduced to a gastrosplenic trunk, the hepatic artery arising from the superior mesenteric artery. The right gastric was given

off by the gastroduodenalis rather than by the hepatic. The dorsal pancreatic arose from the superior mesenteric, and the pancreaticoduodenal arcades were atypical.

This case is an example of a hepatomesenteric trunk, i.e., the common hepatic artery arose from the superior mesenteric artery instead of from a tripodal celiac axis which thus had become reduced to a bipodal gastrosplenic trunk. This modality was found by Michels in 2.5 per cent of cases.

CASE 4. A 6 year old boy was first hospitalized at the age of 5 months for congenital dilatation of the urinary bladder with stricture of the vesicourethral orifice, and congenital hypoplasia of the abdominal wall muscles. At the age of 18 months a permanent suprapubic cystostomy was established after partial cystectomy and resection of the vesical neck. There were many subsequent admissions for urinary tract infections. Cystolithiasis and ureterolithiasis were found when the child was 5 years old. He died of uremia on his eighth admission to the hospital.

Autopsy findings. The duodenum was intraperitoneal being attached to the posterior abdominal wall by a mobile mesoduodenum. The arrangement of the small intestine was a mirror-image of the normal in that it occupied largely the right half of the abdominal cavity and in that the terminal ileum entering the cecum was located in the left lower quadrant. The entire large intestine was on the left side. The ascending colon was mobile being attached to the posterior abdominal wall by a redundant mesocolon. On reaching the diaphragm, it made a sharp downward turn such that the descending colon came to lie behind it. There was no hepatic angulation and thus no defined transverse colon. The sigmoid and rectum were not remarkable. The normal spleen which at this age should weigh about 60 grams was absent. However, an ovoid and multilobular "accessory" spleen 3.5 centimeters in the longest dimension and weighing 11.5 grams was covered by the greater omentum and situated in the angle formed by the ascending and descending colons. There were vascularized adhesions between the greater omentum and the accessory spleen. The heart showed no congenital abnormalities. The lungs including their lobations were normal.

Angiography (Fig. 3). The superior mesenteric artery was normal in its retropancreatic portion. Emerging from behind the pancreas, it described a right instead of a left convex curve giving off the usual branches in mirror-image distribution. The celiac axis was reduced to a hepatosplenic trunk with the left gastric artery arising from the aorta by a nearby but separate ostium. The splenic artery ran along the upper border of the pancreas which it supplied by multiple branches. It terminated in a beaded and tapering fashion before reaching the tail end of the pancreas (Fig. 4). There was no defined left gastroepiploic artery. The right gastroepiploic artery arising normally from the gastroduodenalis gave origin to an accessory middle colic artery.

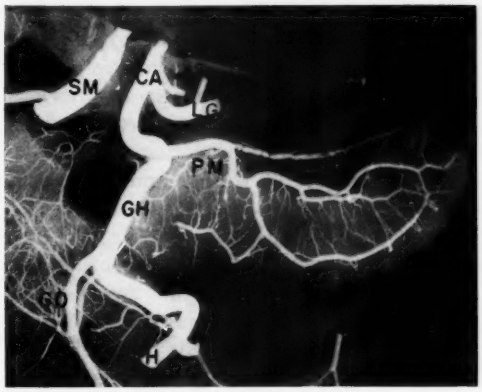


FIG. 4. Case 4. Roentgenogram of pancreas and related vessels which have been filled with radiopaque mass. Note the tapering attenuation of the terminus of the splenic artery.

This case illustrates the association of heterotaxy of the abdominal viscera with abnormalities of splenic development. This association has been emphasized by Aguilar and associates and by Putschar and Manion. Since a spleen of normal location, size, shape, and blood supply did not develop, the present case is viewed as an example of agenesis of the (normal) spleen. An organoid mass of splenic tissue, however, was found in relation to the "splenic" flexure of the colon. Although this mass was appreciably smaller than the normal spleen, it was larger than the usual accessory spleen. The splenic tissue was deeply fissured and consequently multilobulated. These fissures might represent either a fusion of multiple accessory spleens or more probably an incomplete segmentation of an accessory splenic anlage which, if complete, would have resulted in multiple accessory spleens of the usual small sizes. In support of this interpretation, were not only the atypical configuration and the absence of a hilum but also the blood supply, which was via omental vessels in spite of the fact that there

was no agenesis of the true splenic artery. It would be a matter of semantics to object to the designation of the spleen in the present case as accessory just because the normal spleen was absent. At any rate, the deep fissures and multilobularity here found have been emphasized by Brandt and Liebow as one of several types of polysplenia.

The current case is compatible with the concept that at least with respect to the spleen, angiogenesis—splenic artery—and organogenesis are independent of each other. It has to be realized, however, that normally the splenic artery in spite of its name also serves as a major source of blood supply to the pancreas as exemplified by the present case.

CASE 5. The case was of a full term male infant weighing 3,100 grams. Shortly after delivery an operation was performed for the correction of a large omphalocele and left diaphragmatic hernia. The infant died several hours later.

Autopsy findings. The proximal portion of the colon followed a straight course from the right iliac fossa to the splenic flexure, i.e., there was no hepatic angulation and thus no true transverse colon. Beyond this, the large intestine was normal. The mesentery had a single point of attachment high in the posterior abdominal wall, just big enough to allow the passage of the superior mesenteric artery. From here it fanned out as a common mesentery for the small intestine, cecum, and large intestine. The duodenum was mobile on account of a long mesoduodenum and the absence of a transverse mesocolon. Superiorly, the mesoduodenum was continuous with the gastrohepatic ligament—lesser omentum. About the level of the ampulla of Vater there was a wide fold which extended from the posterior—right—leaf of the mesoduodenum to the posterior reflexion of Glisson's capsule and the inferior wall of the foramen of Winslow. The anterior wall of Winslow's foramen was formed by the lesser omentum as usual and by the superior half of the anteriorly displaced duodenum. The lesser omental cavity was normal as was the greater omentum. The pancreas was contained within the mesoduodenum, whose posterior leaf covered the posterior surface of the pancreas up to the level of the celiac axis origin. From this point to the very end of the tail, the posterior leaf was attached to the posterior abdominal wall forming a long and narrow mesopancreas which carried the splenic artery and incompletely divided the lesser omental cavity into two compartments. The anterior leaf blended with the "transverse" mesocolon. The left side of the diaphragm presented a partially repaired defect. The left kidney and left adrenal were located in the lower portion of the left pleural cavity, shifting the mediastinum to the right. The left lung was hypoplastic. The liver was multilobulated and markedly enlarged. Polydactylia was noted in all extremities.

Angiography. The celiac axis was normal except that its gastroduodenalis arose from the superior mesenteric artery. Otherwise the vascular distribution of the abdominal viscera was classical.

A superior mesenteric origin of the gastroduodenalis is a rare variant which was encountered in 1 per cent of 200 adults examined by Michels.

CASE 6. The case was of a premature female infant in whom on the second day after birth cyanosis developed, with respiratory distress and abdominal distention. A roentgenogram showed marked dilatation of the duodenum. Upon exploratory laparotomy the following malformations were encountered: (a) a hepatoduodenal band compressing the second portion of the duodenum; (b) atresia of the fourth portion of the duodenum the blind end of which was located in an approximately normal position but widely separated from the blind origin of the proximal jejunum which lay free in the pelvis; (c) a crescent of abortive mesentery continuous with the transverse mesocolon but unattached to the abdominal parietes; and (d) malrotation of the large intestine, the cecum being high in the right upper quadrant. The baby died a few hours after a side-to-side duodenojejunostomy.

Autopsy findings. The mesentery was a crescent-shaped fold 2 centimeters in its widest part which, without parietal attachment, extended from the blind origin of the jejunum along the small intestine, cecum, ascending colon, and transverse colon where it became finally anchored to the posterior abdominal wall.

Angiography (Fig. 5). The celiac artery was normal. The superior mesenteric artery emerged as usual from beneath the pancreas but entered the transverse mesocolon whence the vessel coursed retrogradely along the ascending colon, cecum, and small intestine terminating at the blind origin of the jejunum by a few exceedingly delicate twigs.

The abnormality may be better understood by recalling that the primitive mesentery is a double-layered partition which extends from the roof of the coelomic cavity to the midventral body wall and which by enveloping the primitive gut becomes divided into a ventral and a dorsal component. The ventral mesentery normally disappears except in relation to the liver—falciform ligament—whereas the dorsal mesentery re-

mains as a continuous structure—definitive mesentery and mesocolon—furnishing mechanical support for the intestine as well as a path for the intestinal vessels and nerves. Faulty development of the primitive dorsal mesentery will result in the absence of the mesenteric root and deprive the superior mesenteric artery of its normal pathway. Normally this vessel is formed by fusion of numerous ventral segmental arteries—omphalomesenteric roots—forming a rich preaortic network within the dorsal mesentery. In the present case, there was segmental dehiscence of the dorsal mesentery at the site where the ventral segmental arteries normally fuse to become the superior mesenteric trunk. Instead, this vessel was formed by the fusion of omphalomesenteric roots located more caudally, i.e., in that portion of the attached dorsal mesentery destined to become the mesocolon.

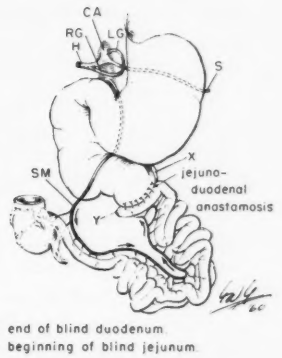


FIG. 5. Case 6. Diagram of abdominal viscera as they appeared after repair of duodenojejunal atresia. Note the retrograde course of the superior mesenteric artery.

DISCUSSION

In Table I we have listed all congenital anomalies encountered in our series of 16 pediatric cases studied by postmortem angiography of the mesenteric arteries. It is noteworthy that in the 6 cases of developmental disturbances of the mesentery—including the mesocolon—and intestine there was also a higher prevalence of congenital anomalies in other organ systems as compared with the 10 control cases of the series. This higher prevalence was most notable in relation to the urinary tract and musculoskeletal system.

In each of the 6 examples of developmental abnormalities of the mesentery and intestinal tract, there was also some abnormality of the mesenteric arterial pattern. In 5, this concerned the celiac arborization which displayed modalities only rarely encountered among adults and not at all observed in any of our 10 control cases. In 4 cases it was the axis itself which was affected, as follows: There was no axis in the first 2 cases, the three stems—left gastric, splenic, and gastrohepatic—arising from the aorta by independent ostia in 1 case and from the aorta and superior mesenteric artery in the other. In Cases 3 and 4 the axis was reduced to a gastrosplenic and gastrohepatic trunk, respectively. In the fifth case the axis itself was normal; the variant concerned the gastroduodenal artery which arose aberrantly from the superior mesenteric artery. It appeared noteworthy and contrary to expectation that even in the cases of congenital malrotation of the intestine any vascular aberration affected the celiac arborization rather than the superior or inferior mesenteric arteries. None of the vascular modalities here described were encountered among the 10 control cases of the series.

Case 6 was the only instance in which the superior mesenteric artery was not only abnormal but also unassociated with any unusual modalities of the celiac arborization. In addition to intestinal malrotation, there was a profound developmental defect of the intestine itself. Duodenojejunal atresia was combined with dehiscence of intestinal continuity the blind end of the proximal jejunum being supplied by a few and exceedingly delicate twigs of the superior mesenteric artery which terminated here after pursuing a retrograde course.

The causation of intestinal stenosis and atresia has often been ascribed to faulty recanalization of the intestinal lumen which at one stage of normal fetal development

becomes temporarily and segmentally occluded by epithelial proliferation. According to Blanc (3), this mechanism applies only to stenoses and atresias in the duodenum since Johnson has shown that the small intestine, other than the duodenum, does not pass through a solid stage during fetal development. In the jejunoileum, atresias are most commonly of the blind-end or cord-like type as in our Case 6 and are thought to result from mechanical injuries incurred in utero. Among such injuries Blanc and associates (4) have singled out intrauterine volvulus resulting among other causes from intestinal malrotation and mesenteric anomalies. This may well operate by a mechanism of ischemia since Louw and Barnard have shown that ligation of mesenteric artery branches in dog fetuses sometime prior to term produces segmental necrosis of the intestine which at birth duplicates the picture of intestinal atresia. The arteriographic findings in Case 6 lend support to this concept by showing that the atresia occurred precisely at a site corresponding to the very terminus of the superior mesenteric artery and which—in conjunction with even minor twisting of the exceedingly mobile small intestine—was most exposed to ischemia. It was here that the vascularity was singularly scant and delicate, and it was this area which was farthest away from the source of arterial pressure head. Apart from the foregoing considerations, the poor vascularization of the blind end of the jejunum in Case 6 has a practical application in suggesting that this segment may not be ideal for surgical anastomoses. This opinion is also held by Louw and Barnard.

SUMMARY

In a series of 16 bodies of children studied by postmortem arteriography there were 6 with congenital abnormalities of the mesentery—including mesocolon—and malrotation of the intestine. In 2 of the 6 cases there was also a diaphragmatic hernia; one was an example of aplasia of the spleen and heterotaxia of the intestines, and in another one there was duodenojejunal atresia. In 5 of the cases vascular aberrations were in the celiac arborization and consisted of anatomic variants encountered but rarely in normal adults and not at all in the 10 pediatric cases which served here as controls. In the case of duodenojejunal atresia the defective small intestinal mesentery was combined with a superior mesenteric artery which ran a retrograde course beginning at the midtransverse colon and terminating about the blind pelvic jejunum.

Congenital anomalies of other systems, notably urinary and musculoskeletal, were more frequent among the 6 cases of anomalies of the intestine and mesentery than in the 10 control cases without such anomalies.

REFERENCES

1. Adachi, B. Quoted by Michels (10).
2. Aguilar, M. J., Stephens, H. B., and Crane, J. T. Syndrome of congenital absence of the spleen with associated cardiovascular and gastroenteric anomalies. Circulation, 1956, 14:520.
3. Blanc, W. A. Personal communication to the authors.
4. Blanc, W. A., Santulli, T. V., and Andersen, D. H. Pathogenesis of jejunoileal atresia. Am. J. Dis. Child., 1958, 98:564.
5. Brandt, H. M., and Liebow, A. A. Right pulmonary isomerism associated with venous, splenic, and other anomalies. Laborat. Invest., 1958, 7:469.
6. Eaton, P. B. The coeliac axis. Anat. Rec., 1917, 13:369.
7. Johnson, F. P. The development of the mucous membrane of the esophagus, stomach, and small intestine in the human embryo. Am. J. Anat., 1910, 10:521.
8. Lipschutz, B. A composite study of the coeliac artery. Ann. Surg., 1917, 65:159.
9. Louw, J. H., and Barnard, C. N. Congenital intestinal atresia; observations on its origin. Lancet, Lond., 1955, 2:1065.
10. Michels, N. A. Blood Supply and Anatomy of the Upper Abdominal Organs; with a Descriptive Atlas. Philadelphia and Montreal: J. B. Lippincott Co., 1955.
11. Pernkopf, E. Quoted by Michels (10).
12. Putschar, W. G. J., and Manion, W. C. Congenital absence of the spleen and associated anomalies. Am. J. Clin. Path., 1956, 26:429.
13. Reiner, L., Rodriguez, F. L., Platt, R., and Schlesinger, M. J. Injection studies on the mesenteric arterial circulation—I, technique and observations on collaterals. Surgery, 1959, 45:820.
14. Tandler, J. Ueber die Varietaeten der Arteria coeliaca und deren Entwicklung. Anat. Hefte, 1904, 25:472.

A CLINICOPATHOLOGIC STUDY OF OBSTRUCTING CARCINOMAS OF THE RIGHT PORTION OF THE COLON

THOMAS C. WILDER, M.D., MALCOLM B. DOCKERTY, M.D., and JOHN M. WAUGH, M.D., F.A.C.S., Rochester, Minnesota

THE OUTLOOK for the cancer patient with a lesion, the removal of which is technically and safely feasible, is estimated by appraising two somewhat intangible factors, namely the resistance of the host and the aggressiveness of the lesion. The latter lends itself much more than does the former to modalities of measurement. Certain types of cancer —carcinoids for example—spread more slowly than do others. Similar varieties of cancer springing from different "soils" behave differently; thus "ordinary" colonic cancer is a lethal growth if it complicates chronic ulcerative colitis. As a prognostic index for recording data on malignant neoplasms affecting hollow viscera like the colon, much help is afforded by the routine use of a classification such as that of Dukes. Many pathologists employ Broders' grading, or a modification thereof, as an aid in predicting the outcome. Invasion of veins, cancerization of perineural lymphatics, and microscopic demonstration of malignant cells in peritoneal fluid are all of prognostic importance. More recently, the discovery of cancer cells in the portal and peripheral blood of patients in whom colonic lesions appear curable by other estimates has come into the limelight.

An attempt has been made in the present study to appraise the effect of colonic obstruction when the causative lesions otherwise appear surgically controllable. The right portion of the colon was chosen since Nickell and Dockerty's previous study from this institution concerned this complication in more distally located lesions.

From the Sections of Surgery and Surgical Pathology, Mayo Clinic, and the Mayo Foundation, Rochester, Minnesota.

Abridgment of thesis submitted by Dr. Wilder to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

LITERATURE

The early literature on obstructing carcinoma of the colon centered chiefly upon the unusually high mortality consequent on attempts to perform one stage resections. Following Sutton's contribution in 1894, surgeons adopted the philosophy of preliminary surgical decompression of the obstructed loop, and the mortality was drastically reduced. The incidence of acute obstruction in a large series, such as that reported by Dennis, approaches 10 per cent for the entire colon while estimates for this complication in the right part of the colon range from 1 to 2 per cent. As pointed out by Karsner and Clark, Ransom, and others, the feature of annularity, which is so conducive to obstruction, is a property of lesions of the left rather than the right portion of the colon. Three additional features militate against the occurrence of obstruction in the proximal reaches of the colon: (1) large luminal diameter, (2) fluidity of the bowel contents, and (3) frequency of incompetency of the ileocecal valve.

It is not surprising, therefore, that Rankin and his associates, in classifying the symptoms of lesions of the right part of the colon list only the dyspeptic, the anemic, and those in which palpation of an asymptomatic mass was the only diagnostic indica-

FIG. 1. Carcinoma, indicated by arrow, of ascending colon which produced complete obstruction. Growth is annular and ulcerative. Note dilatation and hypertrophy of bowel proximal to lesion.

tion of trouble. The symptoms indicating acute intestinal obstruction were considered too rare to merit inclusion in a separate category. A review of the literature failed to uncover any sizeable series in which the primary consideration was given to the problem of completely obstructing carcinomas of the right portion of the colon.

MATERIALS AND METHODS

The files of the pathology section of the Mayo Clinic for the period 1910 through 1943 yielded 20 examples of completely obstructing carcinoma of the right half of the colon. All lesions had been removed with hope of cure, and all of the patients concerned had survived the period of operative mortality. We insisted that the records of both the surgeon and the pathologist be in concurrence with respect to the absolute completeness of the bowel blockage. Many of the 20 patients had required decompressive procedures previously, here or elsewhere, before the growths could be removed.

Two categories were established as controls. One group consisted of a consecutive series of 53 patients with carcinoma of the right part of the colon causing partial obstruction, and the other comprised 73 patients, likewise consecutively observed, in whom the potentially curable carcinoma of the right part of the colon was nonobstructing.

Each of the 146 gross specimens had been carefully preserved in 10 per cent formalin. These specimens were secured and examined for size, type, and gross estimation of the extent of the lesion. The proximal and distal luminal diameters of the bowel were measured and the data recorded. Thicknesses of the bowel musculature above the various lesions were carefully noted. Multiple blocks of tissue were taken from the inner and outer surfaces of the growths, from regional nodes, and from involved blood vessels when the latter were identified. These blocks were paraffin-processed in the usual manner for the making of hematoxylin and eosin sections, which were then added to the original slides on file. Some 500 sections were assembled for microscopic study.

After tabulation of the pathologic data, the clinical histories were secured and analyzed. Finally, a clinicopathologic correlation was effected with special reference to prognosis.

FINDINGS

Location. Most of the acutely obstructing growths were located near the hepatic flexure, whereas the lesions in the control categories were more frequently situated in the cecum and in the ascending colon.

Gross types. Nineteen of the 20 growths in the category of complete obstruction were annular and ulcerative (Fig. 1). The remaining lesion, a cecal neoplasm, was polypoid and necrotic with superficial areas of ulceration. Eighty per cent of those

growths causing partial obstruction were likewise ulcerative and annular, or almost so; the remainder were polypoid, and in some instances intussusception was evident. The nonobstructing lesions displayed the "average" appearance of lesions of the right part of the colon such as might be observed in any unselected series.

Size. A striking difference was noted in the average size of lesions in the 3 categories studied. In general, the growths causing complete obstruction were truly diminutive. Those causing partial obstruction were likewise rather small. The unselected controls, especially the cecal lesions, were, by comparison, large.

Extent. As a measure of lesion aggressiveness, a modification of Dukes' method was adopted, as follows: A lesions, those confined to the mucosa; B_1 lesions, those with involvement of the muscularis only; B_2 lesions, those with peritoneal involvement or invasion of pericolonic fat; and C lesions, those associated with positive findings in the lymph nodes. It was unusual to discover a type C growth that would not simultaneously qualify for a B_2 rating. It is of interest to observe that rather marked degrees of penetration and spread to regional nodes were present in the acutely and partially obstructing lesions even though the primary growths were comparatively small.

Mechanical effects. The thickness of the bowel wall and its circumference were both measured proximal and distal to the growths in the ascending colon and the hepatic flexure (Fig. 2). Cecal lesions were not considered in this analysis since the calculations would have had to be made on the ileum. The data indicate that the anatomic and physiologic changes incident to obstruction in the respective segments studied reached maximal proportions before complete blockage of the bowel was manifested clinically.

Microscopic features. Microscopic classification was patterned after the familiar method of Broders. Higher degrees of anaplasia were, if anything, more manifest in the nonobstructing growths (Fig. 3).

FIG. 2. Closed loop obstruction from lesion of hepatic flexure associated with competent ileocecal valve. Marked cecal dilatation is present.

The tendency to involve blood vessels was not pronounced in any of the categories. However, a meticulous search was not conducted with this feature in mind, and elastic tissue stains were not routinely employed. A notable scirrhous reaction featured the stroma in about one-fifth of the lesions causing acute or partial obstruction (Fig. 4). It was much less frequently noted in the second group of controls in which there was no obstruction. The serious import of such a scirrhous reaction has recently been emphasized by Fahl and associates. Perineural lymphatic involvement was noted in 8 patients with obstructing carcinoma, and in 1 instance this interesting phenomenon was seen in the area of the myenteric plexus (Figs. 5 and 6). Neural and perineural extensions were fewer in the nonobstructing growths.

CLINICAL ANALYSIS

Incidence. Exact figures of incidence are difficult to secure in considering obstruction

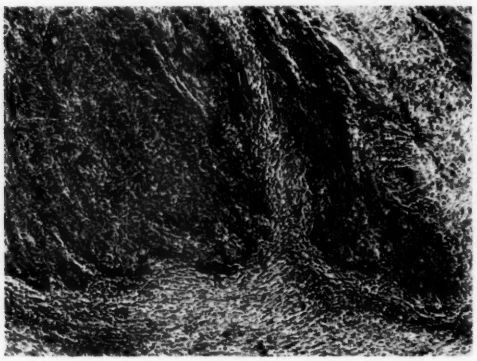


FIG. 3.

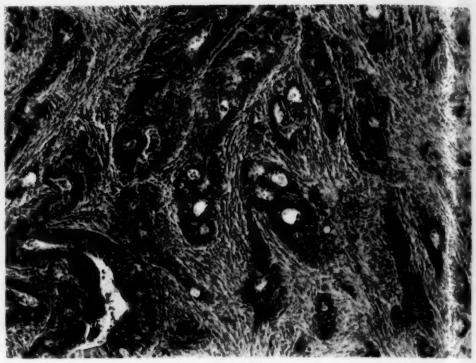


FIG. 4.

FIG. 3. Grade 4 adenocarcinoma from nonobstructing category which, in general, featured higher degrees of anaplasia than did its obstructing counterparts. Hematoxylin and eosin, ×60.

FIG. 4. Grade 2, completely obstructing adenocarcinoma with associated scirrhous reaction of stroma. Twenty per cent of obstructing carcinomas exhibited degrees of fibrosis of this order. Hematoxylin and eosin, ×60.

of a portion of the colon wherein the contents are predominantly fluid. This is particularly true if one excludes, as we did, polypoid growths of low malignant potential which tend to intussuscept. In our experience, lesions of the right part of the colon causing complete obstruction comprised about 1 per cent of our total series.

Sex. In the category of acutely obstructing growths, females outnumbered males in the ratio of 11:9. Twice as many males as females had nonobstructing and partially obstructing growths. This 2:1 predominance of males is the one usually cited in reported series of carcinoma of the right part of the colon.

Age. Ages of the patients ranged from 16 to 82 years with very little by way of intergroup differences, except a slight tendency for acutely obstructing carcinoma to affect persons at an earlier age.

Symptoms. Concerning the various symptoms of which the patients complained, the occurrence of crampy abdominal pains and of constipation, constipation alternating with diarrhea, and nausea and vomiting was prominent among individuals with obstructing lesions. On the other hand, the occurrence of gross melena was noted with about equal frequency in all 3 categories.

On physical examination, abdominal distention, often with borborygmi, was very frequently listed in the categories of obstruction and partial obstruction. A mass was rarely palpable in these instances. By contrast, in the nonobstructing lesions, palpable masses were often located in the right lower abdominal quadrant.

Laboratory data added little to the findings already noted with respect to acute obstruction. Some degree of anemia was present in most of the patients in all groups. Surprisingly enough, hemoglobin determinations indicated comparable degrees of blood loss for the small obstructing and for the larger growths in the second control series. Plain roentgenograms were generally employed in the patients with acute obstruction, but occasionally thin barium enemas were carefully introduced. In these instances the completeness of the colonic blockage was invariably demonstrated roentgenographically.

TREATMENT

Right hemicolectomy in one or two stages was the treatment employed in all of the 146 patients studied. In 16 of the 20 patients with acutely obstructing lesions, a preliminary decompressive procedure was used. Seven

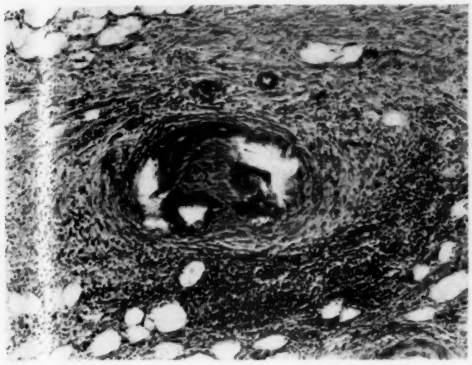


FIG. 5.

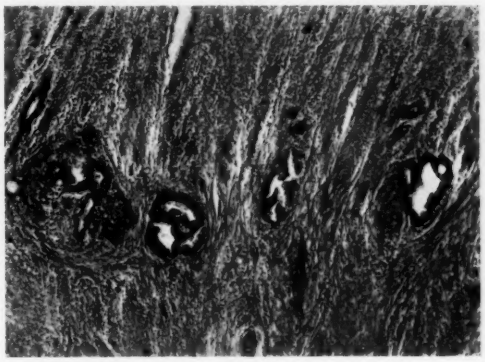


FIG. 6.

FIG. 5. Perineural involvement in a grade 2, acutely obstructing adenocarcinoma of right part of colon. Hematoxylin and eosin, ×75.

FIG. 6. "Selective" invasion of myenteric plexus in an obstructing grade 2 adenocarcinoma of ascending colon. Hematoxylin and eosin, ×48.

of these 16 procedures had been carried out elsewhere, the patients coming to the Mayo Clinic for their definitive resections. In the control groups of patients, one stage hemicolectomy with ileocolic anastomosis was carried out much more frequently. It must be remembered that selection of these cases encompassed an era in which two stage removal of many colonic growths was more or less conventional.

As mentioned in a foregoing paragraph, no case was included wherein death occurred during the accepted period of operative mortality or wherein the original procedure was deemed palliative. This mode of selection was made to permit our appraisal of obstruction, per se, through a comparative 5 year follow-up period.

PROGNOSIS

Five year survival rates reflect the serious outlook in store for those patients with obstructing lesions of the right part of the colon. Neither of 2 patients with acutely obstructing lesions of the cecum exceeded the 3 year mark postoperatively. Acutely obstructing lesions of the hepatic flexure were likewise serious, with only 22 per cent of the patients successfully reaching the 5 year mark. Even in cases involving the ascending colon, a 5 year salvage rate of 33 per cent for patients with acutely obstructing lesions was only half as optimistic as that which featured the outlook for patients in the other 2 groups combined. Patients with partially obstructing lesions were prognostically positioned approximately midway between those with acutely obstructing lesions and the second group of controls without obstruction.

COMMENT

The true incidence of acute obstruction as a complication of carcinomas of the right portion of the colon was not established in this study. Deletions included patients who died in the immediate postoperative period and patients upon whom palliative procedures were carried out. However, even with allowance for these exceptions, the fact that only 20 suitable cases were recorded in the clinic files from 1910 through 1943 bespeaks a very low rate of occurrence for this complication.

Clinically, the 11:9 preponderance of females in our category of complete obstruction is at variance with the 2:1 ratio of males to females for a large unselected series as reported by Mayo and Lovelace. Perhaps examination of a larger group of cases than we had at our disposal might have corrected this apparent discrepancy.

The symptoms presented merit little by way of special comment except perhaps to raise the question why small lesions in the categories of patients with obstruction were of similar duration to those of patients with nonobstructing lesions. Somewhat puzzling, also, was the existence of comparable degrees of anemia shown by patients in all 3 categories. Alvarez and his colleagues were able to relate the severity of anemia to the surface areas of colonic carcinomas. We do not have the answers to these questions.

With respect to location, the hepatic flexure of the colon appeared to pre-empt the severely obstructing growths. This is in keeping with the observations of Dennis and of Gregg and Dixon. Likewise, in accord with the findings of Miller, we noted that partially obstructing growths were often found in the cecum.

Unlike Ransom, we discovered that acute degrees of bowel obstruction were induced, not by large obturating lesions, but by growths that were truly diminutive. Annularity rather than bulk was the feature that compromised the lumen of the bowel in our main study group of 20 patients. The existence rather than the degree of impediment to the flow of bowel contents appears to be the main factor in inducing muscular hypertrophy of the wall and of dilatation of the lumen proximal to the growth. However, severe degrees of obstruction were reflected in a 5 year survival rate only three-fifths as good as that obtained when lesser degrees of obstruction existed.

When an intergroup comparison is made, one finds that on the basis of extent of lesion and of degrees of microscopic anaplasia, a better than average outlook should be predicted for those patients in the categories of obstruction. Our final tabulation shows this to be anything but true. In keeping with observations recorded for lesions of the left part of the colon—and in a much larger series—these small, obstructing growths are extremely serious. For this paradoxical situation we offer only the postulation that the edema and hyperperistalsis which feature intestinal obstruction promote the entrance into and, through milking action, the dissemination of cancer cells along the afferent lymphatics and blood vessels. Our studies indicate that embolization rather than permeation is the important mode of spread, inasmuch as we did not observe unusual degrees of the latter in our material.

SUMMARY

Acutely obstructing carcinomas of the right side of the colon are rarely encountered in surgical practice. A series of 20 such lesions has been collected for study during a 34 year period at the Mayo Clinic. These cases were compared with partially obstructing and nonobstructing counterparts, chosen consecutively as controls.

Aside from certain emergency symptoms manifested by acutely obstructing carcinomas, there was little to set them apart from the others. At operation, the obstructing growths were small and annular with a predilection for the region of the hepatic flexure. Their removal did not present special difficulties, and in all instances in the present "selected" series it appeared to be complete. In spite of gross and microscopic aspects which would lead one to expect a good result, the final 5 year outlook was very serious. Partially obstructing lesions yielded surgical results which were somewhat less somber. Lesions offering little or no impediment to the flow of feces approached the anticipated good outlook generally associated with removal of lesions of the right part of the colon. The seriousness of obstruction as a factor in the prognosis of carcinomas in this region seems to have been established in our study.

REFERENCES

1. Alvarez, W. C., Judd, E. S., MacCarty, W. C., and Zimmermann, A. R. The varying degrees of anemia produced by carcinoma in different parts of the colon. Arch. Surg., 1927, 15: 402–417.
2. Broders, A. C. The grading of cancer. Minnesota M., 1925, 8: 726–730.
3. Dennis, Clarence. Treatment of large bowel obstruction; transverse colostomy—incidence of incompetency of ileocecal valve; experience at the University of Minnesota Hospitals. Surgery, 1944, 15: 713–734.

4. DUKES, C. E. The classification of carcinoma of the rectum. J. Path. Bact., Lond., 1932, 35: 323–332.
5. FAHL, J. C., DOCKERTY, M. B., and JUDD, E. S. Scirrhous carcinoma of the colon and rectum. Surg. Gyn. Obst., 1960, 111: 759–766.
6. GREGG, R. O., and DIXON, C. F. Operable malignant lesions of the colon producing obstruction. Surg. Clin. N. America, 1941, 21: 1143–1152.
7. KARSNER, H. T., and CLARK, BURTON, Jr. Analysis of 104 cases of carcinoma of the large intestine. Am. J. Cancer, 1932, 16: 933–970.
8. MAYO, C. W., and LOVELACE, W. R. Malignant lesions of the cecum and ascending colon. Surg. Gyn. Obst., 1941, 72: 698–706.
9. MILLER, R. T. Cancer of the colon. Ann. Surg., 1923, 78: 209–225.
10. NICKELL, D. F., and DOCKERTY, M. B. The five year survival rate in cases of completely obstructing annular carcinoma of the descending colon and sigmoid; a pathologic study. Surg. Gyn. Obst., 1948, 87: 519–524.
11. RANKIN, F. W., BARGEN, J. A., and BUIE, L. A. The Colon, Rectum, and Anus. Philadelphia: W. B. Saunders Co., 1932.
12. RANSOM, H. K. Carcinoma of the right colon. Surgery, 1939, 5: 340–357.
13. SUTTON, J. B. Cancer of the colon and its treatment. Clin. J., Lond., 1894, 4: 255–258.

PLASMA PROTEIN SYNTHESIS IN THE NORMAL DOG AND AFTER TOTAL HEPATECTOMY

JOHN C. KUKRAL, M.D., JACK D. KERTH, M.D., RONALD J. PANCNER, B.A., DAVID W. CROMER, B.A., and GEORGE C. HENEGAR, M.D.,

Chicago, Illinois

ALL PLASMA PROTEINS are synthesized by the liver except gamma globulins which are presumably manufactured by the reticuloendothelial system.

This current concept is based on experiments which have one or a combination of the following disadvantages: (1) an inadequate method of protein separation, (2) a relatively unphysiologic animal preparation, or (3) a lack of direct biochemical estimates of plasma protein synthesis. For example, in 1947, Tarver and Reinhardt studied serum protein synthesis in normal and hepatectomized dogs using isotope methods to study synthesis and the Howe salting out technique for serum fractionation. The latter method separates the serum proteins into two gross fractions, albumin and globulin. These workers used a one stage hepatectomized dog operated upon under pentobarbital anesthesia in which a prosthetic device was substituted for the intrahepatic vena cava. Studies on these animals were made for 5 hours, and because of the anesthetic used the dogs remained anesthetized throughout the entire experimental period. The data showed that the normal dog produced 20 times more albumin and 7 times more globulin than the liverless animal. These workers, however, doubted whether any significant albumin synthesis occurred in the liverless dogs, because of the probable admixture of as much as 40 per cent globulin by the Howe method of serum protein separation.

From the Departments of Surgery, Northwestern University Medical School and the Veterans Administration Research Hospital, Chicago. Supported in part by the Frederick Augustus Preston Memorial Fund for cancer research.

Miller, Bly, and Bale later investigated the biochemical synthesis of all plasma protein components which were separated by the Howe method and zone electrophoresis. These workers concluded that gamma globulins were the only protein produced extrahepatically. These conclusions were reached as a result of a combination of tracer experiments made on intact rats and acute, 6 hour studies on isolated perfused livers and carcasses.

In 1958, Schenk and co-workers used an improved two stage hepatectomy in dogs which were studied from 8 to 20 hours. These workers noted only 30 per cent decrease in plasma protein concentration after hepatectomy using both the Howe salting out and paper electrophoretic methods for plasma protein separation. Since there was no evidence for increased protein catabolism or marked plasma volume changes, the possibility that some protein was sequestered to extravascular pools was considered. Direct biochemical methods of measuring plasma protein synthesis, however, were not used in their studies.

In the present study an attempt was made to study the comparative roles of hepatic and extrahepatic tissues in plasma protein synthesis by combining improved surgical and biochemical techniques. This combination of techniques permits the comparison of plasma protein synthesis in ambulatory, one stage liverless preparations with the same animals in the normal state. Paper electrophoresis was used for plasma protein separation and the rate of incorporation of labelled amino acid in-

to plasma protein as an index of protein synthesis.

MATERIALS AND METHODS

Radiobiochemical assays were made on labelled plasma protein fractions of 8 adult mongrel dogs. Seven were studied in the normal state, 5 after total hepatectomy, and 2 after sham operation.

Four of 6 dogs served as their own controls, since plasma protein studies were compared in the same animals in the normal state and after total hepatectomy. The same applies to the 2 dogs before and after sham operation. Data on 2 dogs were not included in the statistical analysis for significance but appear in the composite graphs.

Each dog received an intravenous dose of 250 microcuries of methionine labelled with radioactive sulfur(S^{35}). Serial samples of serum and plasma were drawn at intervals of 1, 3, 6, 9, 12, and 24 hours after injection. Serum and plasma samples were analyzed by different methods according to the outline in Figure 1.

The serum samples were analyzed according to the method of Armstrong and co-workers (2) in the following manner. The serum proteins were first separated by paper electrophoresis into albumin, $alpha_1$, $alpha_2$, $beta_1$, $beta_2$, and gamma globulin. These individual proteins were then eluted quantitatively from the paper with dilute ammonium hydroxide and grouped into three gross fractions: albumin, intermediate globulins—a mixture of alpha and beta globulins—and gamma globulin. Each of these three fractions was then precipitated from solution with 50 per cent trichloracetic acid, weighed, and the radioactivity in the protein precipitate counted in a gas flow scintillation counter.

After precipitation of all proteins the amount of radioactivity remaining in the protein-free filtrate was determined as follows: The filtrate of each fraction was evaporated to dryness and brought up to standard volume. Three milliliter aliquots of each filtrate were dried and the residue

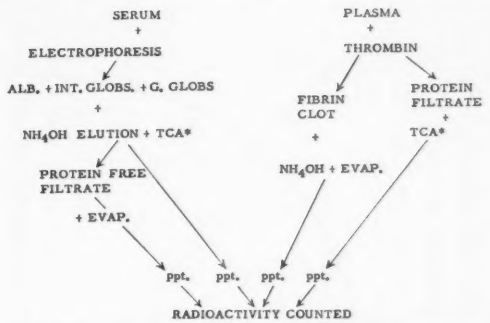


FIG. 1. Bioassay procedures. TCA*, trichloroacetic acid.

counted. The results were expressed as counts per minute per milliliter of the initial volume of protein-free filtrate.

The plasma was analyzed in two steps: Fibrinogen separation was achieved first by adding thrombin to plasma under controlled conditions of *p*H, ionic strength, fibrinogen, and thrombin concentration. The fibrin clot thus formed is almost 100 per cent fibrinogen. This clot was dissolved in concentrated ammonium hydroxide, evaporated to dryness, weighed, and analyzed for radioactivity as a protein precipitate of fibrinogen according to a modification of Jacobsson's method. The second step of the plasma analysis is the precipitation of the serum proteins which remain in solution after the formation of the fibrin clot. These serum proteins were precipitated with 50 per cent trichloracetic acid, dried, weighed, and the radioactivity counted in the precipitate. This combined fraction of serum proteins was designated "total proteins." There were thus 5 total fractions studied—albumin, intermediate globulins, gamma globulin, fibrinogen, and total serum proteins.

After these initial studies, each dog was allowed to remain on a standard diet in a steady metabolic state for 8 to 12 weeks during which time degradation and excretion of the radioactive label took place. Biodecay caused 80 to 95 per cent of the radioactivity to disappear from the animals' tissues in this period. At the end of this time, under ether and oxygen endotracheal anes-

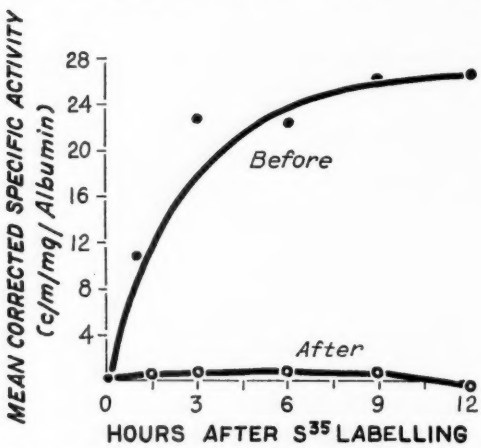


FIG. 2. Incorporation of S^{35} methionine into albumin before and after total hepatectomy.

thesia, a one stage hepatectomy was performed using the technique of Starzl and associates. The liver was mobilized and a portacaval shunt was constructed. The liver was then stripped off the intrahepatic vena cava leaving the vena cava in situ.

These dogs awoke in 5 to 30 minutes after operation at which time a baseline blood sample was drawn to determine the amount of residual radioactivity remaining in the plasma proteins. This was subtracted from the specific activities of the post-hepatectomy experimental period. When the animals were alert and ambulatory and the baseline samples were drawn, 250 microcuries of S^{35}-methionine were given intravenously thus beginning the posthepatectomy experimental period. During this period hourly pulse and respiration rates were recorded and hematocrits were determined every 3 hours. Glucose solution was given intravenously to prevent hypoglycemia. Serial samples of serum and plasma were drawn and analyzed in the same manner as in the normal state. The counts per minute of radioactivity were corrected for layer thickness of the precipitate and for physical decay. All results were expressed as corrected counts per minute per milligram of each fraction. This quantity of corrected counts per minute per unit weight of protein or unit volume of protein-free filtrate is referred to as the specific activity. A synthesis curve for each fraction may be obtained by plotting the specific activity versus time. Each graph shown in Figures 2, 3, 4, and 6 represents the composite synthesis curves of 5 dogs.

The specific activities of the protein-free filtrates were plotted as "utilization curves" after hepatectomy in 4 dogs (Fig. 7) and in 1 dog before and after hepatectomy (Fig. 5). Data on the fraction designated "total protein" were not plotted separately but appear for comparison in a summarizing figure of the peak specific activities of all fractions in all dogs (Fig. 8). Data of the sham operated on dogs were expressed in terms of average per cent synthesis of the normal state.

RESULTS

In the normal dog a rapid progressive rise in radioactivity was noted in all fractions of plasma proteins after the intravenous injection of the labelled amino acid. The peak specific activity in counts per minute per milligram of protein fraction, was attained in 6 to 12 hours followed by a gradual decline.

A corresponding progressive decrease in specific activity with time was noted in the protein-free filtrate, the "utilization curves." These reached low levels at roughly the same time as the peak specific activity of the synthesis curves. This is seen by comparing Figure 4 with Figure 5 and Figure 6 with Figure 7. The specific activity in the albumin and fibrinogen fractions was practically absent in the liverless animals as compared with the animals in the normal state. These results are shown in Figures 2 and 3.

After hepatectomy only the gamma globulin fraction showed a rise in specific activity similar to that in the normal state, but there were notable differences in the contour and height of the synthesis and "utilization" curves (Figs. 4 and 5). The significance of this will be discussed.

The intermediate globulins, which are a mixture of alpha and beta globulins, show approximately one-third of the prehepatectomy specific activity in the liverless state. There was a corresponding rapid disappearance of radioactivity from the protein-free filtrate of the intermediate globulins in 4 dogs after hepatectomy. The synthesis and utilization curves for the intermediate globulins are shown in Figure 6 and 7.

The total protein fraction synthesis curves in 3 dogs were similar to the intermediate globulin curves in contour but the magnitude of synthesis after hepatectomy is somewhat higher. These curves are not shown because of the similarity to the intermediate globulin synthesis curves but the data appear in the summarizing Figure 8. The range of the maximum average specific activities for all protein fractions before and after hepatectomy are graphically illustrated in Figure 8.

The solid horizontal lines represent the mean peak specific activities of each fraction before hepatectomy and the horizontal broken lines represent the same mean values after hepatectomy. The vertical solid lines which connect the solid dots and the open circles indicate a paired experiment of synthesis of each protein fraction before and after hepatectomy in the same 4 animals, whereas those vertical lines connecting the solid dots and open triangles indicate the same studies in 2 different animals, 1 before hepatectomy and 1 after hepatectomy, not previously tagged.

Comparison of the relative heights of each horizontal line in each fraction, therefore, represents the relative amounts of maximum specific activity found in each fraction after removal of the liver as compared with the normal state. These differences of synthesis before and after hepatectomy, when compared in the same animals, are statistically significant. The p value for each fraction was less than 0.01.

To obtain the per cent synthesis which occurs in the liverless dogs compared with the same animal in the normal state, the

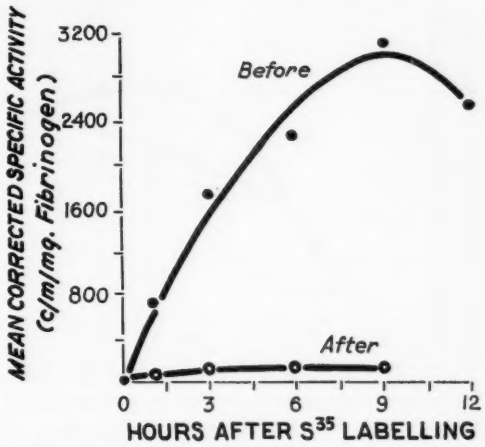


FIG. 3. Incorporation of S^{35} methionine into fibrogen before and after total hepatectomy.

ratios of the relative heights of the solid horizontal lines to the height of the broken horizontal lines are multiplied by 100. These values for each fraction are as follows: fibrinogen, 20 to 2,800 times 100 = 0.7 per cent; albumin, 0.4 to 28 times 100 = 1.4 per cent; intermediate globulins, 20 to 58 times 100 = 35 per cent; gamma globulin, 125 to 100 times 100 = 125 per cent; and total proteins, 35 to 90 times 100 = 40 per cent.

In contrast, the mean per cent specific activity remaining in each plasma protein fraction after a sham surgical procedure in 2 dogs when compared with the normal state in the same animals was as follows: fibrinogen, 110 per cent; albumin, 100 per cent; gamma globulins, 90 per cent; intermediate globulins, 95 per cent; and total proteins, 105 per cent. The difference of synthesis for each fraction after sham surgery as compared with the same normal animals was not statistically significant. The p value for each fraction is greater than 0.4.

The animals remained alert and ambulatory and maintained urinary output. The experimental period or the time from S^{35}-methionine injection to the end of the plasma protein experiment was 12, 13, 15,

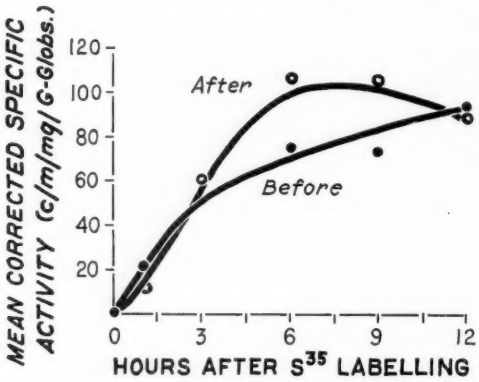


FIG. 4. Incorporation of S^{35} methionine into gamma globulin before and after total hepatectomy.

26, and 12 hours for 5 dogs. The actual survival period was longer or 15, 16, 21, 30, and 18 hours, respectively, because no studies were begun until the dogs were fully awake, and at the first sign of bleeding or clinical deterioration no further samples were drawn for plasma protein studies. Tachycardia above 140, drop in hematocrit, comatose state, or frank bleeding from an abdominal drain were indications to discontinue the plasma protein studies, although all the animals were observed until death. Bleeding tendencies became more troublesome after 18 hours of survival, and all dogs had some blood in the peritoneal cavity at necropsy. This finding probably is a reflection of the rapid depletion of fibrinogen stores in the hepatectomized dog and deserves further comment because of some indirect evidence observed in this study.

It is of interest that although our data show that both albumin and fibrinogen production is almost absent after hepatectomy, actual depletion of fibrinogen stores is manifest much sooner than depletion of albumin. There was practically no fibrinogen in the plasma of 4 dogs as early as 12 to 16 hours after hepatectomy, without frank hemorrhage, whereas albumin was present in only slightly diminished quantities at 16 to 30 hours after hepatectomy in 3 dogs. This finding supports the concept that fibrinogen has a smaller pool size and a more rapid turnover than albumin. Early fibrinogen depletion may also be a reflection of the magnitude of surgical trauma of hepatectomy, because fibrin is needed in early healing and hemostasis. These fibrin clots may constitute a reservoir of fibrinogen, which, when finally depleted, gives rise to the hemorrhage so frequently noted as the terminal event in hepatectomized dogs. The speculation that the fibrin clot is a dynamic entity has been proposed before, but direct evidence of this concept is lacking.

DISCUSSION

The results will be discussed under three broad headings: (1) the isotopic technique for the study of plasma protein synthesis, (2) alterations of physiology after hepatectomy, and (3) the accuracy of the electrophoretic technique for plasma protein separation. However, only those aspects of these headings which pertain to the interpretation and possible sources of error in the data of the present study will be covered.

ISOTOPIC INCORPORATION AND PROTEIN SYNTHESIS

Prior to the use of radioisotopes the method of measuring plasma protein production after hepatectomy was by the quantity of a given protein present before and after organ removal. This approach has two major drawbacks: (1) the measure of any biologic quantity gives no true indication of the dynamics of the biochemical processes of synthesis or degradation and (2) changes in blood or plasma volume encountered during or after organ removal can introduce errors in these levels due to hemoconcentration or hemodilution. If we assume, for example, that the total amount of albumin circulating in an average dog is 100 grams, that the total amount of fibrinogen is 10 grams, and that the animal is in a steady state producing as much albumin and fibrinogen as it destroys, then the levels of these

proteins will not change. Let us further assume that the animal produces and destroys 5 grams of albumin and 5 grams of fibrinogen per day. If production suddenly stops and degradation continues at the same rate, as probably is the case in the liverless dog, then all the albumin would be gone in 20 days and the total fibrinogen would disappear in 2 days. Therefore, under these conditions, if one were to measure the circulating albumin and fibrinogen levels 24 hours after hepatectomy, the actual values would be 95 grams or 95 per cent of albumin left and 5 grams or 50 per cent of fibrinogen left. Actually, total circulating albumin and fibrinogen cannot be determined by routine laboratory techniques. This example is used only to illustrate a point.

One might conclude from these figures that the role of the liver in albumin production is only a small proportion of that for fibrinogen, when actually the liver probably synthesizes 100 per cent of both proteins. Thus, actual measurements of plasma protein levels may be misleading. Similarly, fluid shifts during hepatectomy introduce another error of interpretation which can be seen from the next example. If we assume a large fluid loss during hepatectomy, consisting mainly of fluid poor in proteins, such as lymph, the early net effect will be concentration of the remaining plasma proteins. By routine laboratory determinations the levels of albumin and fibrinogen in grams per cent will be greater. Conversely, the loss of protein-rich fluid, such as blood, will lead to hemodilution and a low level of proteins in terms of grams per cent. In the case of those proteins produced purely extrahepatically, such as gamma globulin, low levels due to hemodilution might erroneously suggest a drop in synthesis when actually their production is not altered. The use of isotopic tracers for measuring protein synthesis has minimized these drawbacks, since the amount of radioactivity per unit weight of plasma protein or specific activity is a reflection of the synthesis rate and is unaffected by compartment size changes due to fluid shifts alone. Protein shifts which accompany fluid shifts can affect the specific activity and will be discussed later.

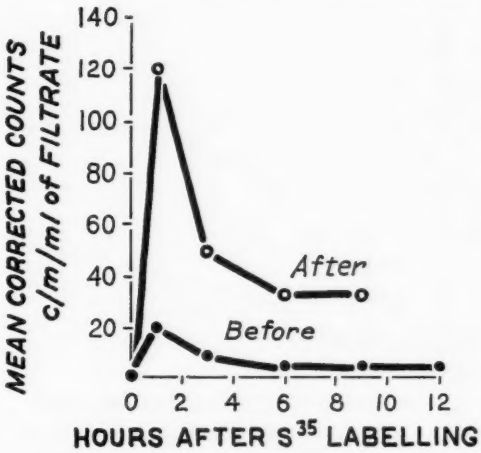


FIG. 5. Utilization of "free methionine pool" before and after total hepatectomy in 1 dog.

A labelled amino acid is particularly suited to estimate plasma protein synthesis because amino acids are the exclusive building blocks of all proteins. The rate of incorporation of S^{35}-labelled methionine, a sulfur-containing amino acid, into the plasma protein molecule, therefore, is an index of plasma protein synthesis. This has been shown to hold true in the normal as well as the hepatectomized dog, since the metabolic pathways of methionine leading to other tissue proteins as well as serum proteins remain intact in the liverless dog. Supportive evidence for protein synthesis from incorporation data is obtained by simultaneous data on utilization of the amino acid building blocks. This is based on the assumption that the utilization of labelled amino acids to make protein comes from a common metabolic pool which is depleted of the label during the course of protein synthesis. Thus, both the incorporation or uptake of a labelled component into the finished product as well as the utilization or disappearance of the component is evidence for synthesis. A simplified version of this concept is expressed by the following

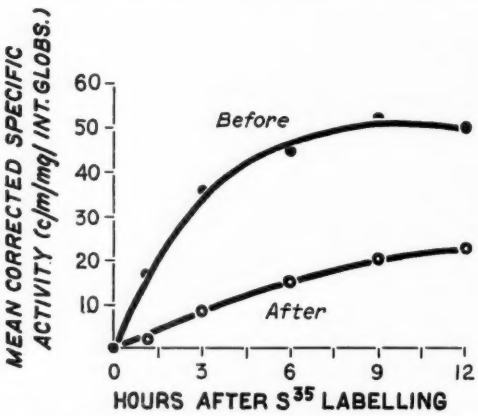


FIG. 6. Incorporation of S^{35} methionine into intermediate globulins before and after total hepatectomy.

equation which was modified from the work of Reiner.

$$A^* + B = P^*$$

Where:

- A^* = any number of labelled amino acids, such as S^{35}-methionine
- B = any number of other amino acids
- P^* = labelled plasma protein molecules, containing a specific number of A^* and B

Plasma protein, P^*, is in dynamic equilibrium, as shown by the reversible equation, with a pool of the building blocks which were used to make the finished product. Therefore, both the amount of radioactivity incorporated into P^* as well as the amount of radioactivity remaining in A^* are an index of the rate of synthesis of P^*.

Sulfur-containing amino acids are present in all plasma proteins but some plasma proteins contain a greater proportion of these amino acids than do others. Comparison of the synthesis rates of various plasma proteins when using S^{35}-methionine as the tracer amino acid must therefore take into account the relative amounts of sulfur and sulfur-containing amino acids in each purified protein fraction. The amount of radioactivity in P^*, a specific plasma protein molecule will, therefore, depend on the proportion of A^*, or S^{35}-methionine, incorporated into P^*.

Comparison of synthesis rates of fibrinogen, gamma globulin, and albumin are calculated by utilizing the data of this study (Fig. 8) and from the data given by Phelps and Putnam. From Figure 8 it can be seen that fibrinogen incorporates about 30 times more radioactivity per gram than does gamma globulin, but there is 3 times more methionine in fibrinogen. The total specific activity is present in 3 times as much methionine; therefore, the synthesis rate is one-third the incorporation rate; so that in the normal dog fibrinogen is synthesized about 10 times faster than gamma globulin. Similarly, fibrinogen is produced approximately 50 times faster than albumin in the normal dog, since there is 2,800 to 28 or 100 times the specific activity in fibrinogen as compared to albumin, but also about twice as much methionine for the same weight. These calculations are based on the assumption that S^{35}-methionine is incorporated into plasma protein in an unchanged form and that the S^{35} is not transferred to other sulfur-containing amino acids as cystine and cysteine. If all sulfur-containing amino acids, methionine, cysteine, and cystine, are used in these estimates it would appear that fibrinogen is synthesized even faster in comparison to gamma globulin and albumin. The true value probably lies somewhere in between these two extremes.

The intermediate globulins and total protein fractions in the normal dog are not included in the comparison of synthesis rates, because these fractions are a mixture of several proteins and comparison would be meaningless. Similarly, no attempt was made to translate the utilization data into comparative synthesis rates, since these filtrates may not represent pure amino acids from a common pool. Exact analyses of the protein-free filtrate were not made in this study. This filtrate was arbitrarily termed "free methionine pool" after a similar designation by Garrow, in the realization that

this filtrate may contain, in addition to free methionine, small polypeptides or other metabolic fragments which may carry the S^{35} label. Although preliminary chromatographic analyses show this filtrate to be mainly methionine, the disappearance of this radioactivity may represent incorporation of methionine into other tissue proteins, a process not affected by the absence of the liver. Regardless of the exact chemical nature of the protein free filtrate the disappearance of its specific activity is correlated with an increase in the plasma protein specific activity and may be taken as supportive evidence for plasma protein synthesis, as is shown by comparing Figures 6 and 7. Thus, in the liverless state, incorporation of S^{35}-methionine into the intermediate globulins was evidence for synthesis of these proteins as shown by the convex synthesis curve. Further evidence for this synthesis was a disappearance of the probable precursors which reached a low level of specific activity at approximately the same time that the highest specific activity was attained in the intermediate globulins.

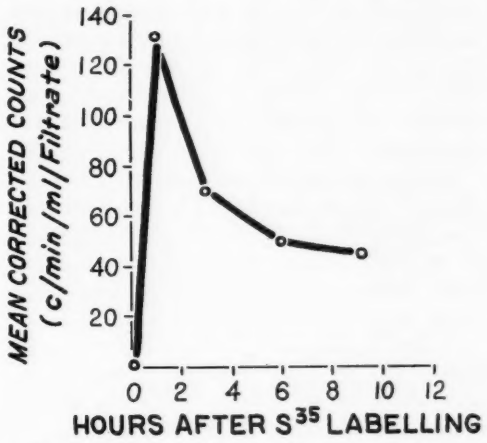


FIG. 7. Utilization of "free methionine pool" following total hepatectomy in 4 dogs.

ALTERATIONS OF PHYSIOLOGY AFTER HEPATECTOMY

One question is whether or not the hepatectomized dog is a good physiologic preparation for the study of plasma protein synthesis. This question arises because organ ablation studies are always hampered by the creation of associated abnormal physiologic conditions, many of which are difficult to separate from the primary organ function being studied. The hepatectomized animal is a prime example of this, since the liver is capable of so many interrelated biochemical processes. For example, if only the role of the liver in plasma protein synthesis were under study, then ideally the removal of this organ would alter only this synthesis pattern, and all other biochemical processes would remain intact. Other processes, however, may be altered, introducing possible variables into the hepatectomy study, some of which are difficult to control. A consideration of these variables as they apply in this study is pertinent.

SURGICAL STRESS

Many of the metabolic effects of surgical stress are well documented, but little is known of the effects of surgery upon plasma protein synthesis. Assessment of this variable upon plasma protein synthesis was made by the use of a sham operation on 2 dogs. Instead of studying plasma protein synthesis before and after a hepatectomy, these studies were made before and after a 70 per cent gastrectomy with portal vein dissection simulating the portacaval shunt procedure of hepatectomy. These animals showed no significant differences in any plasma proteins synthesized after the sham operation as compared with the same studies in the same animals before the sham operation. This indicated that surgical stress alone was not the major factor in altering the plasma protein synthesis seen after hepatectomy.

Another facet of the effects of operation upon protein metabolism is the possible role that the surgical procedure may have upon tissue breakdown and mobilization of previously tagged metabolic precursors. The tissue catabolism that follows operation is well

known; therefore, in a previously tagged animal subjected to operation the reutilization and synthesis of tagged "metabolic fragments" into plasma protein must be considered. This probably did not occur in any significant amount for the following reasons.

1. The amount of radioactivity in all the tissues is small after 8 to 12 weeks because of rapid biologic degradation and excretion of the label; thus, there is little substrate from which tagged metabolic fragments could originate.

2. There was no significant difference in the residual activity of plasma protein samples taken prior to anesthetizing the animal before hepatectomy or sham operation as compared with the residual specific activity right after either operative procedure, just before tagging for the postoperative experimental period. This observation suggests no great mobilization of tagged metabolic fragments as a result of either of the surgical procedures.

3. Similar patterns of all plasma protein synthesis were seen whether or not the hepatectomized animal had some residual radioactivity in the tissues. For example, in 1 animal which was not studied first, by tagging with S^{35}-methionine in the normal state a similar pattern of posthepatectomy synthesis was noted in all fractions, especially of gamma globulin and intermediate globulins, as was seen in all other animals which were tagged before and after hepatectomy 8 to 12 weeks apart. This is illustrated in Figure 8 by noting lengths of the vertical lines of any one fraction which connects the open circles and solid dots and the open triangles and solid dots. The similarity of the lengths of these lines suggests that differences in synthesis that follow hepatectomy are similar, regardless of the presence of residual tissue radioactivity.

THE EFFECT OF POSSIBLE PROTEIN POOL SIZE CHANGES

Although it has already been pointed out that gross changes in blood and plasma volume shifts leading to hemoconcentration or hemodilution would not theoretically alter incorporation data expressed as specific activity, since the counts per minute per unit weight of protein remain the same, no matter how dilute or concentrated the solution, another facet of pool size changes deserves mention. This factor has to do with changes in the size of the plasma protein pool due to rapid extravasation of plasma proteins. It is well known that plasma proteins exist partly extravascularly and partly intravascularly, with a dynamic interchange between the two pools. A blood sample taken, for example, after a large shift of fluid from the vascular tree might be accompanied by a large intravascular shift of unlabelled proteins, especially albumin, to maintain oncotic pressure, thus giving a lower radioactivity per milligram of total albumin. A more rapid exchange of albumin radioactivity with thoracic duct lymph has been demonstrated by Schenk and associates after hepatectomy, indicating a more rapid loss of albumin into lymph. The reasons for this loss are not clear, but some speculation on this point will be made when the relative merits of one stage hepatectomy are discussed.

Some evidence of pool size changes is seen in the gamma globulin data of the present study. This evidence is not interpreted in terms of large shifts of plasma protein in or out of the vascular tree but rather is attributed to "relocation and compression" of amino acid pools. The shapes of the gamma globulin synthesis and "utilization" curves are different in the normal and liverless dog (Figs. 4 and 5), most likely on the basis of (1) decreased amino acid catabolism and (2) redistribution of the amino acid pool to the remaining tissues engaged in protein synthesis after hepatectomy. The role of the liver in amino acid catabolism is well known; thus, the hepatectomized animal retains a higher concentration of "free amino acids." It is further presumed that removal of an organ as large as the liver, which is essentially a large amino acid and protein reservoir, would diminish the general amino acid pool size. Thus, in the normal state the peak

specific activity of 100 for gamma globulin was attained at about 12 hours in contrast to a peak specific activity of 125 attained 6 hours after hepatectomy. Higher specific activity is noted also in the protein free filtrate after hepatectomy, indicating a greater specific activity of the free methionine pool in the liverless dog than in the same normal animal (Fig. 5). Another explanation for these differences may be stimulation of the reticuloendothelial system after the surgical stress of hepatectomy. This explanation, however, is not supported by any significant change in gamma globulin synthesis after sham operation.

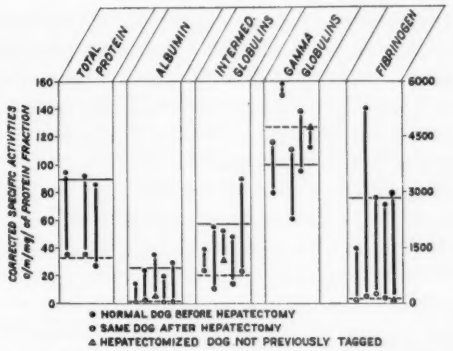


FIG. 8. Peak specific activities of various S^{35} labelled canine plasma protein fractions before and after total hepatectomy.

ONE STAGE VERSUS TWO STAGE HEPATECTOMY

A two stage hepatectomy preparation has certain disadvantages over its one stage counterpart in the study of the plasma protein metabolism, even though no data are available which compare plasma protein synthesis by these two techniques. These probable disadvantages are: (1) a greater over-all loss of blood and lymph, and (2) a greater chance for qualitative alterations in plasma proteins to occur.

The two stage hepatectomy procedure leads to greater fluid loss as a result of operation, because the first stage of a two stage hepatectomy is performed to create collateral vascular channels by partial occlusion of the portal vein. The second stage operation is carried out in a field rich in collateral blood and lymph vessels and in which tissue planes are not as sharply delineated because of the fibrous reaction to the previous first stage operation. Securing hemostasis may be more difficult, and raw tissue surfaces rich in lymph channels which could ooze a significant amount of lymph during and after the second stage operation may be created. The possible effects of large lymph losses on the size of plasma protein pools by extravasation of protein into extravascular spaces has already been mentioned. In any procedure in which the possibilities of compensation for large lymph losses are present, plasma protein shifts may accompany fluid shifts into the extravascular space. This may be true of albumin shifts in particular, since this protein is mainly responsible for oncotic pressure equilibrium. Such albumin shifts, although theoretic, may partially explain the finding of a more rapid equilibration of I^{131}-albumin with thoracic lymph in the two stage hepatectomized dog compared with the normal.

In the one stage hepatectomy utilized in this study, some of these possibilities are controlled by the following fine points in technique. Lymphatic vessels, when encountered, were minimal in number because of absence of previous operation. Those that were encountered were easily ligated with fine silk. Most lymphatic channels were found along the portal vein, especially in its pancreatic course, at the time of construction of the portacaval shunt prior to actual liver extirpation. The portacaval shunt was performed with a minimum amount of portal vein mobilization and thus less raw tissue surface was exposed. Furthermore, for similar reasons the shunt was constructed as far caudad as possible to avoid too much pancreatic dissection. Estimated blood loss during operation was 30 to 100 milliliters and occurred during the removal of the liver from the vena cava. Attempts to strip the liver from the vena cava have been attended by large blood losses in the past. Vascular clamps above and below the liver isolated the intra-

hepatic vena cava and enabled one to ligate each hepatic vein and repair tears in the vena cava in a relatively bloodless field. The vena cava thereby remained in situ and no prosthetic device was needed. Blood loss was replaced during operation about 1 hour prior to the injection of S^{35}-methionine and the beginning of the experimental period. Thereafter no more fluids were given except dextrose by small injections to prevent hypoglycemia.

The amount of fluid given postoperatively to hepatectomized animals is critical, since some glucose must be given to prevent hypoglycemia, but an improper amount of fluid may lead to alterations of plasma volumes. Continuous and intermittent intravenous infusions were both used in our study. Usually 4 to 6 milliliters of 50 per cent dextrose were diluted in 20 milliliters of normal saline and given every 30 to 60 minutes. The total intake was therefore about 500 to 1,000 milliliters of water with 50 to 150 grams of glucose in normal saline. Although no blood volume studies were made, evidence for gross fluid shifts such as changes in serial hematocrit determinations or increases in pulse rate was not found. Schenk and co-workers studied blood volume changes after a two stage hepatectomy and found little change when the fluid administered did not exceed 1.2 liters per 24 hours.

The second possible drawback of a two stage hepatectomy in plasma protein metabolism studies is the greater chance that abnormal proteins are produced. The metabolic effects on plasma proteins that follow partial occlusion of the portal vein or the first stage operation are not known. The work of Schenk and co-workers showed qualitative abnormalities in the migration of $alpha_2$ globulins which may be related to haptoglobin formation. This abnormality of $alpha_2$ migration may occur between the first and second stages of hepatectomy as a result of partial occlusion of the portal vein. In the one stage preparation of the present study such an abnormality or any migration abnormality was not seen in over 100 electrophoretic analyses. This discrepancy is probably caused by differences in technique of the two hepatectomy methods, since sufficient time elapsed for abnormal globulins to be produced between the first and second stages of hepatectomy but not after the one stage procedure. Clinically, this is analogous to the production of abnormal globulins in certain disease states; for example, Bence-Jones globulins may not appear in the serum electrophoretic pattern of clinically suspected cases until late in the course of multiple myeloma, according to Armstrong (1).

Two other possibilities of abnormal protein production should be mentioned. These are biologic abnormalities not detectable by electrophoretic analyses but which may be detected only by other more specific methods, as immunochemical or ultracentrifugal techniques. For example, from Figure 6 it is seen that about one-third of the globulins of intermediate mobility, $alpha_1$, $alpha_2$, and beta globulins, are produced by extrahepatic tissues after the liver is removed. The possibility that extrahepatic tissues may not synthesize intermediate globulins under normal circumstances but do so only under stress of a liverless state cannot be ruled out from our data. Further immunochemical studies may be necessary to rule out this possibility.

BIOLOGIC ACCURACY OF ELECTROPHORESES

Even though the electrophoretic technique remains as one standard of plasma protein separation, some inherent drawbacks of this technique in biologic work as they apply to this study deserve mention. The biologic nonhomogeneity of plasma proteins based solely on electrophoretic migration patterns is well known. Many biologically unrelated proteins, such as fibrinogen and some forms of Bence-Jones protein, may migrate at similar speeds between gamma and beta globulin. Conversely, many biologically related proteins may migrate at different speeds. Thus, although most forms of antibody migrate in the gamma globulin position, some antibody may be found in the $alpha_2$ and beta globulin position. The latter

example, therefore, pertains to this discussion because gamma globulin or antibody admixture may be a possible source of error in this study. This admixture most likely does not account for all the radioactivity in the intermediate globulins after hepatectomy because:

1. It is noted that even if over 50 per cent of the antibody protein migrated with the intermediate globulins there would still be significant specific activity in the intermediate fraction after hepatectomy, not attributable to gamma globulin or antibody admixture.

2. Gamma globulin by weight constitutes a much smaller portion of the serum proteins than do the combined intermediate globulins, even though the specific activity is higher. It is therefore difficult to account for approximately one-third radioactivity by weight occurring in the intermediate globulins on the basis of gamma globulin admixture alone.

3. Data on total serum proteins in 3 dogs indicate 40 per cent synthesis after hepatectomy, which is much too high to be accounted for by gamma globulin alone. The protein migrating in the gamma globulin position from our data constitutes only 10 to 15 per cent of the serum proteins by weight as contrasted to 30 to 35 per cent of the intermediate globulins.

On the other hand, the small but detectable amount of radioactivity in the albumin, 1.4 per cent, and fibrinogen, 0.7 per cent, fractions probably does represent slight admixture and adsorption encountered during the separation process. This slight admixture and adsorption are known to occur during the most ideal biochemical protein separations.

SUMMARY AND CONCLUSIONS

The highly significant differences in plasma protein synthesis between animals in normal and liverless states are most likely due to the absence of functioning liver parenchyma. In spite of the possible drawbacks mentioned, the alert, ambulatory, liverless animal preparation performed in one stage is a more physiologic preparation than isolated perfused organs or carcasses for the short term, 24 hour study of extrahepatic plasma protein synthesis. A one stage preparation, as used in this study, may have certain advantages over a two stage preparation. In the normal dog, fibrinogen synthesis occurs approximately 50 times faster than albumin and 10 times faster than gamma globulin. In the hepatectomized dogs there is virtually no albumin or fibrinogen synthesis but as much or more gamma globulin synthesis than the same animal in the normal state. Albumin and fibrinogen are thus purely hepatic in origin, whereas all gamma globulin originates extrahepatically. These findings substantiate the works of Miller and Tarver and their associates. The extrahepatic origin of other globulins besides gamma globulin has not been previously reported in any animal and may result from species differences or to the other possibilities mentioned. More biochemical studies are needed in order to characterize these proteins fully and to determine their origin; however, some preliminary conclusions can be drawn:

The 1 stage hepatectomized dog is a good preparation for the study of plasma protein synthesis. These studies, when combined with identical studies in the normal state, indicate that (a) the synthesis rate of fibrinogen is 50 times greater than albumin and 10 times greater than gamma globulin in the normal dog; (b) all albumin and fibrinogen in the dog is synthesized by the liver; (c) all gamma globulin is synthesized extrahepatically; (d) about one-third of the intermediate globulins, a mixture of alpha and beta globulins, are also synthesized outside the liver; and (e) the exact source of this extrahepatic synthesis remains unknown.

REFERENCES

1. ARMSTRONG, S. H., JR. Personal communication regarding unpublished data.
2. ARMSTRONG, S. H., JR., MCLEOD, K., WOLTER, J., and KUKRAL, J. The persistence in the blood of the radioactive label of albumin, gamma globulins, globulins of intermediate mobility studied with S^{35}

and paper electrophoresis; methods and preliminary results. J. Laborat. Clin. M., 1954, 43: 918–937.
3. Garrow, J. S. The effect of protein depletion on the distribution of protein synthesis in the dog. J. Clin. Invest., 1959, 38: 1241–1250.
4. Jacobsson, K. I. Studies on the determination of fibrinogen in human blood plasma. Scand. J. Clin. Lab. Invest., 1955, 7 (Supp. XIV): 7–54.
5. Miller, L. L., Bly, C. G., and Bale, W. F. Plasma and tissue proteins produced by non-hepatic rat organs as studied with lysine and C^{14}; gamma globulins the chief plasma protein fraction produced by non-hepatic tissues. J. Exp. M., 1954, 99: 133–153.
6. Phelps, R. A., and Putnam, F. W. Chemical composition and molecular parameters of purified plasma proteins. In: Plasma Proteins edited by F. W. Putnam. Vol. I, p. 143. New York: Academic Press, 1960.
7. Reiner, J. M. Study of metabolic turnover rates by means of isotopic tracers. Arch. Biochem., 1953, 46: 53–99.
8. Schenk, W. G., Jr., Schreiber, M., Leslie, M. B., Portin, B. A., Mesmer, R. E. G., and Stewart, J. D. The alteration in plasma proteins resulting from total hepatectomy. Ann. Surg., 1958, 148: 401–409.
9. Starzl, T. E., Bernhard, V. M., Benvenuto, R., and Cortes, N. A new method for one stage hepatectomy for dogs. Surgery, 1959, 46: 880–886.
10. Tarver, H., and Reinhardt, W. O. Methionine labelled with radioactive sulfur as an indicator of protein formation in the hepatectomized dog. J. Biol. Chem., 1947, 167: 395–400.

EDITORIALS

THE ULTRASCIENCE OF THE VASCULAR GRAFT

SIGMUND A. WESOLOWSKI, M.D., Brooklyn, New York

THE SINGLE DECADE that has passed, since the introduction of the concept of the synthetic mesh vascular graft, has taken place in an apparent exploded time scale, as a result of the large quantity of work and intense controversy engendered by the decision of the choice of vascular graft material. Ten years ago it was believed that nearly any porous graft constructed of a number of synthetic materials was acceptable. There followed a period of activity characterized by the raiding of dry goods stores, draperies, and old shirts for materials to be used as vascular grafts. Such nondiscriminatory taste naturally and justifiably evoked the reactionary forces of caution. Indiscrimination went underground, reappearing in the more sophisticated, and hardly recognizable, form of the development of commercial vascular graft materials constructed from specifications established by assumption, platitude, and indirection. This was the stage of leasing of the surgical rights of development to the industrial technician who, though demonstrating the best of faith, was at a loss to pass judgment upon the specifications which were given him.

The industrialist deserves great credit, however; in spite of unusual requests to weave and to knit basically unmanageable filaments and yarns, he was able to develop a number of psychologically acceptable commercial grafts. The consuming public of surgeons was then bombarded with successive waves of sales brochures outlining the mystical advantages of various grafts in terms of biologic reactivity, indestructibility at temperatures absurdly in excess of the physiologic, and healing data based upon pitifully short term results. In spite of this transcendence of science into ultrascience, such thinking had the same beneficial effect as an artificial egg, which often stimulates the laying of good eggs by the squatting hen. Ultrascience takes over when science cannot yield the solution—in this case, the specifications for the ideal synthetic vascular graft.

During this same period of time a new preparation was being developed which has proved to be vital in the rapid, simultaneous screening of the equivalent long term fates of all available vascular graft materials; this is the preparation of the growing pig. Studies over the past 3 years have led to the establishment of reasonable specifications for the ideal synthetic vascular graft. Ultrascience fell when science asserted itself by the demonstration that biologic reactivity of the material is not a detectable limiting factor governing the ultimate fate of the vascular graft but that the porosity of the graft wall appears to be the first limiting factor. The type of material is important, therefore, mainly as regards durability of the filament and size of interstice.

In the light of this knowledge, is it disturbing to consider, in retrospect, that the initial period of dry goods implantation was in fact as scientifically sound as the period of commercial development?

From the Department of Surgery, State University of New York, Downstate Medical Center and the Vascular Surgical Service, Kings County Hospital, Brooklyn.

REFLUX ESOPHAGITIS AND HIS'S ANGLE

DAVID H. WATKINS, M.D., F.A.C.S., Denver, Colorado

To INSURE the aboral transfer of food from the esophagus into the stomach and to minimize the effects of acid peptic regurgitation, the junction between these two organs is augmented by a group of structures known collectively as the cardiac mechanism. This mechanism includes the valvular device at the cardiac orifice and the diaphragmatic pinchcock action of the right crus of the diaphragm. The valvular mechanism of the cardiac orifice, or the "hiatal valve," consists of the synergistic action of the oblique inosculation of the esophagus into the stomach, the angle of His, and the difference in intraluminal pressure between the stomach and the esophagus.

Regurgitation and belching are common physiologic events in normal man which demonstrate that the cardiac valve mechanism may be incompetent normally. Regurgitation is prone to occur when esophageal intraluminal pressure falls below intragastric or intra-abdominal pressure. The intraluminal pressure of the esophagus is negative at most times, and, thus, a continuous reflux of stomach contents would occur except for the "hiatal valve." The peristaltic wave offers the increment in energy to increase the intraluminal esophageal pressure to a level above that in the stomach. The valve then opens, and the bolus enters the gastric lumen. When the increment in pressure produced by the peristaltic wave passes off, the intragastric pressure becomes higher than the intraesophageal, the mucosal folds are approximated, and the valve closes.

If this cardiac mechanism becomes disturbed by pathologic development such as a sliding esophageal hiatal hernia, or by surgical means such as cardioplasty, or esophagogastrostomy for obstruction lesions at the esophagogastric junction, the undesirable effects of peptic esophagitis appear.

The angle of His at the incisura is maintained by a loop of gastric muscle, just deep to the mucosa, which passes around the cardia and down each side of the lesser curvature. The earliest description of this muscle comes from Thomas Willis of Oxford, who not only described the loop but showed it in a drawing dated 1674.

Congenital or acquired changes of the gastroesophageal junction such as cardiofundal malformations, sliding hiatal hernia, and congenital short esophagus which lead to reflux esophagitis are characterized by an enlargement of the angle of His and formation of a gastroesophageal funnel. If the cardia is displaced superiorly, then the contractile activity of the stomach mantle, or Willis's muscle, is no more capable of hindering reflux. The valvular function is abolished. This simple dynamic mechanical fact, which has been established by radiologic, experimental, and operative evidence seems to prove that the integrity of the esophagogastric angle of His is fundamental. Flattening of the angle represents the most striking, and sometimes the only, apparent characteristic in the majority of diseases causing reflux esophagitis.

Decisive significance in the genesis of gastroesophageal reflux is to be ascribed to the angle of His and the ancillary mechanisms which aid in its maintenance. The preservation of the oblique, acute-angled inosculation of the esophagus into the stomach, which in the normal state is preserved by the cardiofundal muscular and ligamentary apparatus and the integrity of the esophageal hiatus, is the essential factor in the hindering of reflux.

THE SURGEON AT WORK

DISK THERMAL EXCHANGER

ROD C. PERKINS, A.B., Indianapolis, Indiana

IT HAS BEEN A PRACTICE in many centers to combine the use of hypothermia with extracorporeal circulation and total cardiopulmonary bypass. Various methods by which body temperature can be reduced have been utilized. The present study concerns a method by which the large surface area of the conventional disks of an oxygenator can be utilized simultaneously to control temperature and to oxygenate the extracorporeal blood.

DESCRIPTION OF APPARATUS

The unit is basically a Kay-Cross disk oxygenator with certain modifications of the disk and axle. The prototype model consists of a pair of conventional Kay-Cross end plates, one of which is modified to receive a slightly oversized axle (Figs. 1 and 2). The functional part of the unit consists of a hollow axle which is 1.5 inches in diameter and holds 47 disks—9 inch oxygenator—which are separated by a space of 0.14 inch. These disks are 1/50,000 inch in thickness and have a diameter which is the same as the regular disks. The edge of the center holes of the disks were extruded so that better apposition of disk to axle could be attained. These disks are permanently placed on the axle by a pressure fit. The disks and axle are made of high thermal conductivity copper. The surface of this unit was first covered with a silver electroplate which was later found to be unsatisfactory from a maintenance standpoint and has subsequently been replated with kanigen nickel. This surface can then be siliconized. In each

From the Department of Surgery, Indiana University School of Medicine, Indianapolis.
Aided by a grant from the James Whitcomb Riley Memorial Association.

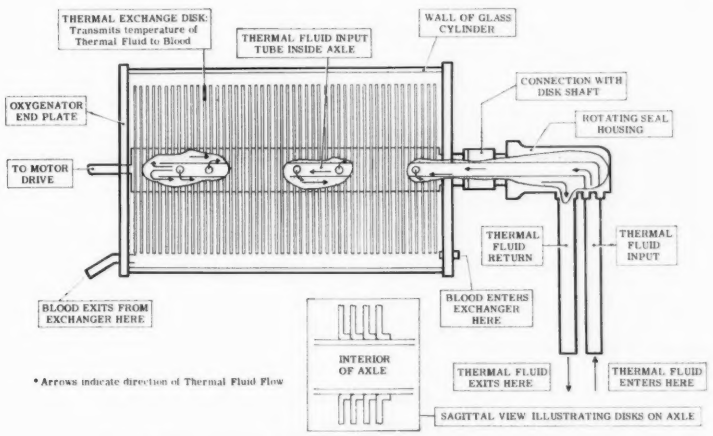

THERMAL EXCHANGE DISK: Transmits temperature of Thermal Fluid to Blood
THERMAL FLUID INPUT TUBE INSIDE AXLE
WALL OF GLASS CYLINDER
CONNECTION WITH DISK SHAFT
ROTATING SEAL HOUSING
OXYGENATOR END PLATE
TO MOTOR DRIVE
THERMAL FLUID RETURN
THERMAL FLUID INPUT
BLOOD EXITS FROM EXCHANGER HERE
BLOOD ENTERS EXCHANGER HERE
INTERIOR OF AXLE
THERMAL FLUID EXITS HERE
THERMAL FLUID ENTERS HERE
* Arrows indicate direction of Thermal Fluid Flow
SAGITTAL VIEW ILLUSTRATING DISKS ON AXLE

FIG. 1. Diagram of disk thermal exchanger and oxygenator.

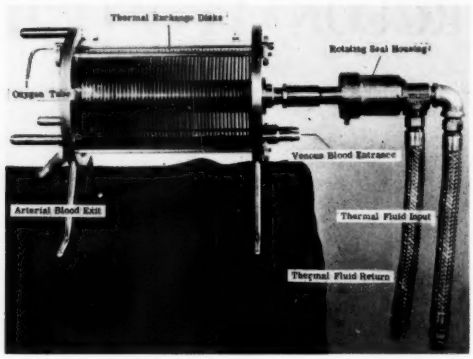


FIG. 2.

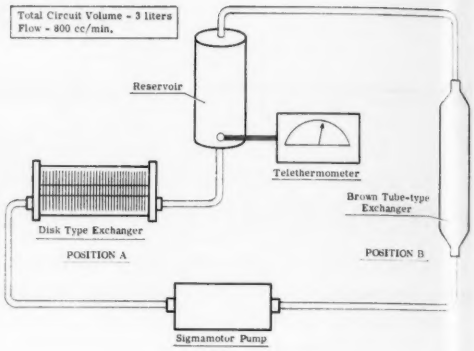


FIG. 3.

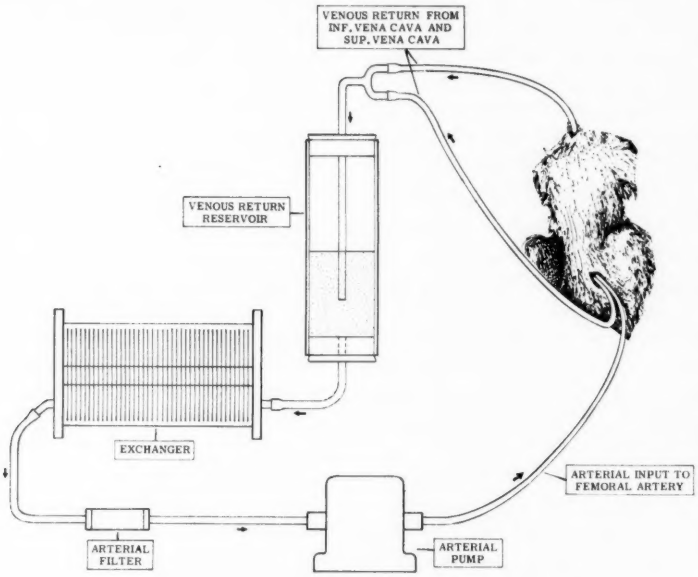


FIG. 4.

FIG. 2. Photograph of apparatus.

FIG. 3. Experimental setup for testing alternately the thermal heat exchanger and the tube type exchanger.

FIG. 4. Partial bypass circuit used in testing the thermal disk exchanger.

end of this hollow axle is a threaded stainless steel plug. One plug has a solid axle attached, the other has a hollow axle. A rotating valve and seal arrangement is attached to the end of the hollow axle. This seal allows the entrance and exit of thermal fluid to and from the interior of the axle while the disks are turning through the blood in the usual manner. The thermal fluid of desired temperature may be from any source: chiller, heater, tap water, or mixing valve. Utilization of this method permits the axle and disks to assume the temperature of the thermal fluid and to transfer this approximate temperature to the blood passing over the disks.

The unit is easily cleaned by placing the axle and disks on a special stand. A small motor is

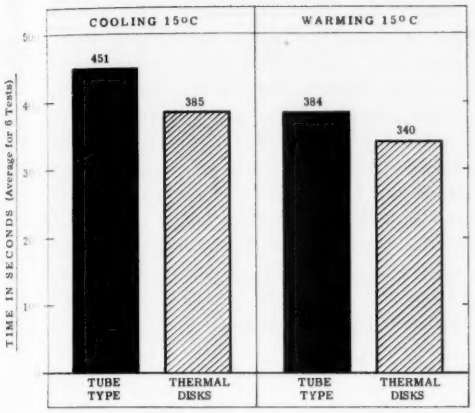


FIG. 5.

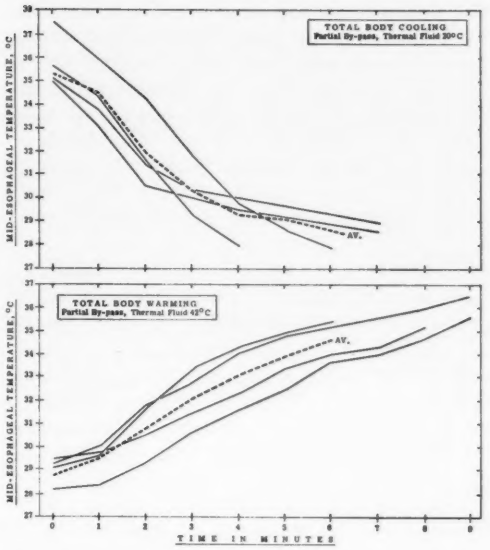


FIG. 6.

FIG. 5. Chart showing average time for cooling and warming water 15 degrees C. with thermal disk and tube type heat exchangers.

FIG. 6. Chart showing representative cooling and warming curves of dogs on partial cardiopulmonary bypass using disk exchanger.

used to rotate the disks while a series of thin spiral brushes are lowered horizontally into the interspaces between the disks.

RESULTS OF STUDY

To evaluate the thermal exchange capacity in a practical manner a closed circuit was established using a Brown tube type exchanger, the disk exchanger, a sigmamotor pump, and a tygon tube reservoir (Fig. 3). The circuit contained 3 liters of water which were circulated at 800 cubic centimeters per minute. The thermal fluid was supplied from a tap water mixing valve to both exchangers separately. With the disk exchanger in position A the circuit was cooled 15 degrees C., from 35 to 20 degrees C. After the temperature was well stabilized the water was warmed 15 degrees C., from 20 to 35 degrees C. This procedure was repeated 3 times. The thermal fluid was then applied to the Brown heat exchanger in position B and the same procedure was repeated. The exchangers were then interchanged so the disk exchanger occupied position B and the Brown exchanger position A, and the same cooling and warming procedure was carried out as before. The time required for each exchanger to change the temperature of the circuit 15 degrees was recorded. These figures were then averaged for each exchanger separately. The results are illustrated in Figure 5. The thermal disk exchanger actually cooled and warmed the priming water somewhat more rapidly than did the conventional tube type exchanger.

To evaluate the method in vivo, mongrel dogs with an average weight of 14.9 kilograms were used. A sigmamotor pump was employed with a flow rate of 50 cubic centimeters per kilogram per minute. The venous return was via the inferior and superior venae cavae with catheters inserted through the femoral and external jugular veins. The arterial catheter was placed in the femoral artery. The partial bypass circuit is illustrated in Figure 4. The circuit was primed with freshly drawn heparinized blood. Temperature measurements were made from an esophageal thermister. The method was nonsterile.

The dogs were cooled to a level of moderate hypothermia with a thermal fluid of 20 degrees C. After stabilization at about 28 to 29 degrees C. they were rewarmed using a thermal fluid of 42 degrees C. Figure 6 depicts representative cooling and warming curves in several dogs, the perfusion of which was not complicated by venous return problems or bubbling. Effective cooling and warming were accomplished rapidly.

Bubble formation in the oxygenator was encountered in several cases. The exact cause was

not fully determined, but blood levels above the axle and areas of worn silver plating on the original disks were believed to be contributory factors. After the disks were replated with kanigen nickel 3 studies were made. Surface bubbling was not encountered when the blood levels remained below the axle, and there was only mild transitory bubble formation when blood levels were raised so that blood passed over the axle.

SUMMARY

A new method of thermal exchange for use with the disk type oxygenator in extracorporeal circuits has been developed. The basic design and thermal exchange mechanism have been presented along with preliminary studies regarding relative thermal efficiency and in vivo trials using the prototype model. This disk method is believed to be advantageous because it requires no increase in priming volume, eliminates the need for special thermal control equipment in the circuit, and can be applied to currently popular disk oxygenators. This preliminary study involved a small 9 inch oxygenator. The same principle can be utilized for oxygenators of any desired size.

TOTAL ABDOMINAL HYSTERECTOMY BY THE MAYO CLINIC (MASSON-COUNSELLER) TECHNIQUE

RICHARD E. SYMMONDS, M.D., F.A.C.S., JOSEPH H. PRATT, M.D., F.A.C.S., and JOHN S. WELCH, M.D., F.A.C.S., Rochester, Minnesota

TOTAL HYSTERECTOMY, whether performed vaginally or via the abdominal route, is a relatively simple operation. Nevertheless, year after year without diminution, we have continued to encounter in our referred gynecologic practice 20 to 25 posthysterectomy fistulas involving the vagina—excluding those related to radiation therapy, radical hysterectomy, and all other causes except total hysterectomy. Injury or ligation of the ureters has been equally common at the pelvic brim, with the ovarian vessels, and at the level of the uterine vessels, but vesicovaginal and rectovaginal fistulas have been much more frequent.

Most of these fistulas and injuries we consider to be results of inadequate abdominal incisions, poor exposure, and—of greater importance—the temerity of the surgeon who fails to dissect adequately the bladder or rectum and to identify the ureters when in doubt regarding their position. It can be stated that, in the absence of radiation changes, practically all fistulas that follow total abdominal hysterectomy are the result of a "blind" placement of suture or ligature or of some unrecognized injury to poorly exposed ureters, bladder, or bowel. The rare injury that might result from careful dissection and mobilization of these structures is recognized and promptly repaired; and given even minimal treatment, it heals without fistulization. With respect to reparative processes the bladder and ureters, when neither ignored nor overtreated, are among the "kindest" of tissues the surgeon contacts.

Many reports of techniques for abdominal hysterectomy specify that to avoid the bladder and ureters, clamps on the uterine vessels must be placed "close to the uterus" or "parallel with the cervix," or that dissection should remain "intrafascial." While this may be desirable in the presence of simple benign conditions, such measures often become difficult or impossible with large or fixed pelvic tumors, such as fixed ovarian lesions, endometriosis, or residuals of inflammatory disease, and may be highly undesirable in other situations, for instance, endometrial and cervical cancer, in which a wide hysterectomy or a substantial vaginal cuff or both are required.

The uterine arteries are no more formidable, no more difficult to isolate and ligate than those encountered in other localities, such as the inferior thyroid, cystic, gastroduodenal, and gastric arteries, where contiguous important structures are subject to injury. Why, then, has so much time and space been devoted to methods of ligating these small vessels? Why can a competent operator observe and control profuse bleeding from an episiotomy, a vaginal laceration, or an atonic uterus and yet all too frequently lose all semblance of composure upon the appearance of comparatively trivial brisk bleeding from a severed or lost uterine artery? The only logical explanation is fear of the nearby ureter. Although this structure has provoked much comment in both the teaching and the execution of techniques for total abdominal hysterectomy, the general policy with respect to the ureter has been negative: it is to be avoided —neither seen nor touched.

Hence the ureters remain unknown, in a sense, to many experienced surgeons who have developed hysterectomy techniques that are quite satisfactory in other respects. Surgeons will dissect and demonstrate the recurrent laryngeal nerve, the hepatic artery, and bile ducts—even the ureter during certain operations on the colon; and yet they will clamp the uterine vessels and close the vagina blindly, assuming rather than demonstrating that the ureters and bladder base are out of danger.

In view of the continuing incidence of surgical

From the Section of Surgery, Mayo Clinic and Mayo Foundation, Rochester.

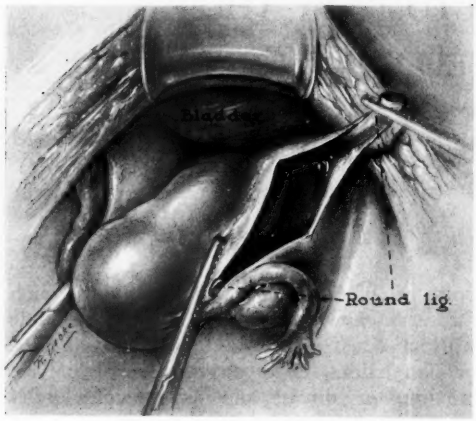


FIG. 1. Forceps applying traction to uterus and to divided round ligaments.

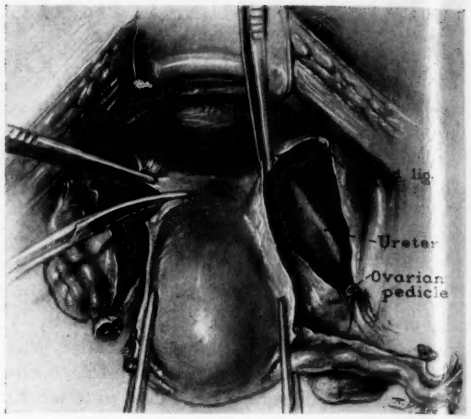


FIG. 3. Vigorous cephalad traction on uterus for mobilization of bladder.

injuries to the bladder, ureters, and rectum, it seems imperative that the teaching of techniques for total abdominal hysterectomy be revised. Rather than mere warnings, the young surgeon needs emphasis placed upon safe routine methods to identify, to visualize, and, when necessary, unhesitatingly to mobilize these contiguous structures.

For the insecure, ureteral catheters may facilitate identification of the ureters. This "crutch," as a rule unavailable when needed most, is impractical and impossible for many surgeons to obtain. Furthermore, routine catheterization of the ureters not only carries some risk but also provides a hard surface against which the ureter can be traumatized more easily. In our opinion it is entirely unnecessary. The ureter always can be identified easily at the pelvic brim or above the usual limit of pathologic involvement and then be traced inferiorly as necessary to obviate the need for catheters.

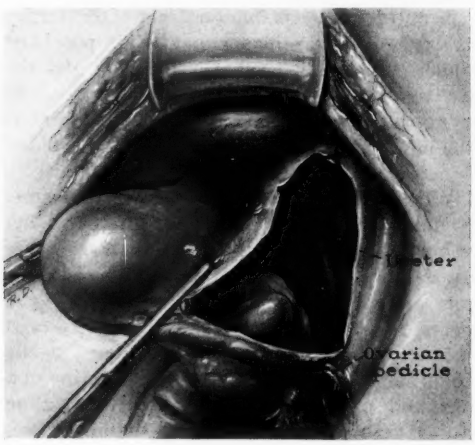


FIG. 2. Isolation of utero-ovarian ligament, tube, and ovarian pedicle. Identification of ureter at pelvic brim.

Except for minor modifications, the technique of total abdominal hysterectomy to be reported has been used at the Mayo Clinic for more than 30 years. Originally developed and briefly reported by Masson, the technique emphasizes 3 points: (1) Constant visualization and knowledge of the position of all structures subject to injury provide safety with simplicity. (2) In possession of this information, the surgeon can manage any unanticipated bleeding without hurried blind suture ligature or clamping and moreover can increase the extent of the operation as indicated by the pathologic condition without fear of damage. (3) The necessarily individual requirements for adequate support of the vaginal vault can be satisfied. Counseller modified the procedure considerably. Its many desirable features have led us to use this technique, with minor individual variations, to the exclusion of other methods with which we had had experience previously.

TECHNIQUE

The vagina is prepared by scrubbing with green soap solution and then is painted with

merthiolate or an equivalent antiseptic solution. A retention catheter is inserted in the bladder and preliminary dilatation and curettage are performed. A long lower midline abdominal incision is utilized. For additional exposure it may be extended superiorly around the umbilicus; but more importantly, the skin incision must be carried well down over the pubic symphysis. Without benefit of this feature the retractor used to spread the incision would elevate the lower end of it, hindering exposure. After thorough, systematic exploration of all abdominal viscera, a Balfour retractor is inserted. The patient is then placed in moderate Trendelenburg position and, after freeing of any adhesions present, a moist abdominal pack is inserted beneath the upper abdominal wall to keep the operative field unobstructed.

Straight forceps are placed across the cornual portions of the uterus, including the round ligament, tube, and utero-ovarian vessels. In addition to preventing back-bleeding later during the operation, continuous traction on these instruments will make the entire dissection much easier and safer. The uterus is pulled up and to the left by the surgeon. The right round ligament is clamped, divided (FIG. 1), and ligated near the uterus. The ligature is left long, tagged with a forceps, and allowed to hang outside the abdomen to maintain exposure.

The peritoneum above and below the round ligament is incised, thus opening the anterior leaf of the broad ligament in the avascular area. The posterior leaf of the broad ligament is opened behind and below the level of the utero-ovarian ligament, either with finger pressure or by the tip of the scissors. The left index finger is passed through this aperture to lift the tube and ovary (Fig. 2). If the latter are to be preserved, the utero-ovarian ligament and tube are clamped, divided, and ligated near the uterus. Otherwise, the finger traction under the tube and ovary assists in the identification and isolation of the ovarian vessels, the infundibulopelvic ligament, and elevates them from the contiguous ureter. To avoid injury the latter must be identified before the ovarian vessels are clamped, cut, and ligated.

The ureter has a fairly constant position, and regardless of catheterization it always can be identified easily at the pelvic brim where it crosses the iliac vessels. In thin patients the ureter can be seen shining through the peritoneum just medial to the ovarian vessels. Scratching the peritoneum overlying the ureter will promote peristalsis, an additional aid to its identification. In obese patients the posterior medial leaf of parietal peritoneum can be grasped between thumb and forefinger and the character-

FIG. 4. Lateral traction on uterus. Clamping of uterine vessels and cardinal ligament at side of cervix after identification of ureters and bilateral displacement, isolation, or both.

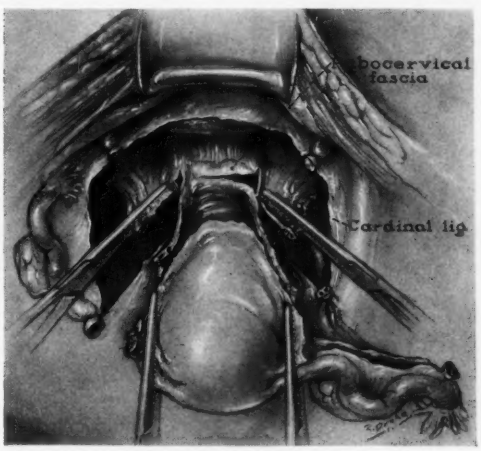


FIG. 5. Anterior traction on uterus. Separation of uterus from peritoneum, rectum, and uterosacral ligaments.

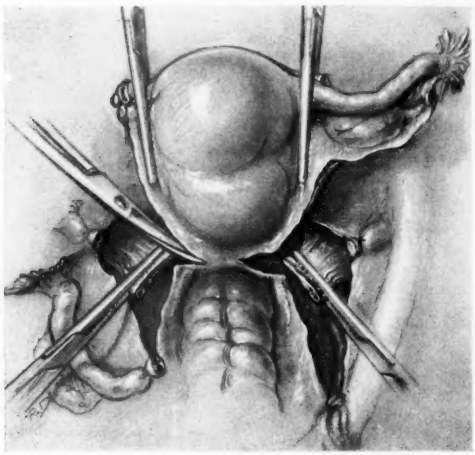


FIG. 6. Incision and slight displacement of pubocervical fascia. The bladder is mobilized 1 to 2 centimeters below this level.

istic "snap" of the ureter can be noted; or with a curved forceps placed on the edge of the peritoneum for medial traction, the ureter can be exposed easily by spreading of the overlying extraperitoneal areolar tissue with the tip of the scissors.

Routine identification at the level of the pelvic brim makes it easy to trace the ureter inferiorly whenever difficult dissection or a question of ureteral position is encountered. Still attached to the peritoneum the ureter is followed to the point where it passes under the uterine artery. If a wide hysterectomy is planned, the ureter at this time can be displaced laterally in its tunnel beneath the uterine artery by spreading the tip of a curved forceps or merely by finger pressure above and medial to the ureter.

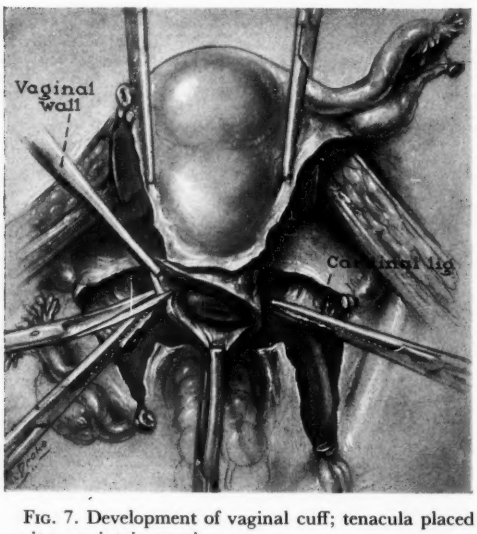


FIG. 7. Development of vaginal cuff; tenacula placed on it to maintain traction.

The same process is repeated on the left to ligate the round ligament and ovarian vessels there, the uterus being pulled and rotated to the opposite side by the first assistant as necessary to maintain tension on the structures being dissected.

With vigorous cephalad traction on the uterus the bladder is now mobilized (Fig. 3). Incision of the vesicouterine peritoneal reflection joins those openings in the peritoneum previously made when freeing the round ligaments. A gauze-covered finger easily frees the bladder from the cervix and anterior vaginal wall; sharp dissection, if necessary, displaces it from the uterine vessels laterally. That the bladder curves upward in this region deserves emphasis. For safe ligation of the uterine vessels, for safe closure of the vaginal angle, and for easy identification of the lower portion of the ureters, it must be mobilized. By careful dissection this can be accomplished with little bleeding.

Further, it must be emphasized that at least 1 to 2 centimeters of the vagina are exposed below the level of planned vaginal transection. The dissection of the bladder with exposure of more than adequate vaginal wall can be accomplished easily at this stage of the operation, whereas it becomes quite difficult once the structure used for traction, the uterus, has been removed.

With the bladder base under direct vision and the ureters readily identifiable throughout their course, the remainder of the procedure can be performed with equanimity. Any inordinate amount of bleeding can be suppressed accurately, without blind clamping or suturing. While the strong traction on the uterus is maintained, first to the left and then to the right, Ochsner forceps are placed well down on the right and left sides of the cervix and at approximately a 45 degree angle to it, clamping both the uterine vessels and the superior portion of the cardinal ligaments (Fig. 4). The tip of the instrument engages the endopelvic—cervical—fascia on the lateral aspect of the cervix immediately above

the vaginal fornix. When the tip of the forceps is undercut or pushed down a bit, a fascial window is opened whose anterior edge is pubocervical fascia, subsequently to be managed as a separate layer.

As mentioned previously, in the presence of endometrial cancer the clamps on the cardinal ligaments and uterine vessels are placed more laterally, the ureter having been previously displaced somewhat, and the dissection remains extrafascial.

If desired, a second Ochsner clamp can be placed on the uterine vessels close to the lateral surface of the uterus to prevent back-bleeding. However, double clamping of the proximal end of the uterine vessels is entirely unnecessary. This so-called safety measure merely crushes additional tissue and takes up more of the relatively little space available between the cervix and the ureter.

The uterosacral ligaments, made prominent by pulling the uterus up and anteriorly toward the symphysis, can be cut with the intervening peritoneum. At the proper place near the uterus there are no significant vessels in this uppermost medial end of the uterosacral ligament, and since the stump of the ligament is easily identified later, clamping or ligation is entirely optional. In the presence of vigorous uterine traction, the peritoneum, rectum, and uterosacral ligaments are easily mobilized and with little bleeding can be pushed down off the cervix and posterior vaginal fornix (Fig. 5). However, if a generous vaginal cuff is planned or if the rectum is adherent, the rectum should be mobilized more extensively from the posterior vaginal wall at this time.

The cervical fascia is incised anteriorly, joining the two fascial windows, and pushed down slightly on the anterior vaginal wall as a separate layer (Fig. 6). The vagina is entered, preferably posteriorly, and the uterus is removed by circumcising the cervix as closely as possible, placing Henrotin vulsellum forceps successively at 3, 6, 9, and 12 o'clock positions on the vaginal cuff as it is developed. These forceps do not include pubocervical fascia anteriorly nor peritoneum posteriorly (Fig. 7). Note that no attempt has been or should be made to place a clamp across the lateral angles of the vagina below the cervix. Clamping of the tissue in this area shortens the vagina, devitalizes the cuff, and endangers the bladder and lowermost portion of the ureter as it swings medially over the anterior vaginal wall. Furthermore, if the clamps on the uterine vessels and cardinal ligaments have been properly placed, vessels in the so-called bloody angle of the cuff are adequately controlled.

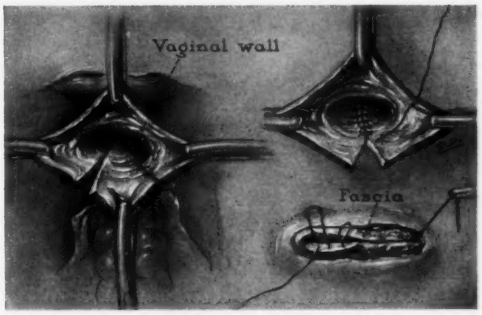


FIG. 8. Closure of vaginal vault. Left, Excision of wedge of redundant tissue and of cul-de-sac peritoneum in presence of potential or actual enterocele. Upper right, Suture closing wedge includes vaginal wall and rectovaginal fascia. Lower right, Closure of vault by everting continuous subcuticular suture that also ligates small vessels in vaginal angle. Both ends of the suture illustrated here are utilized for traction and the suture is continued.

Traction on the vulsellum forceps elevates and exposes the vagina, facilitating the closure of the vault with constant visualization of the bladder base and rectum. A moist laparotomy

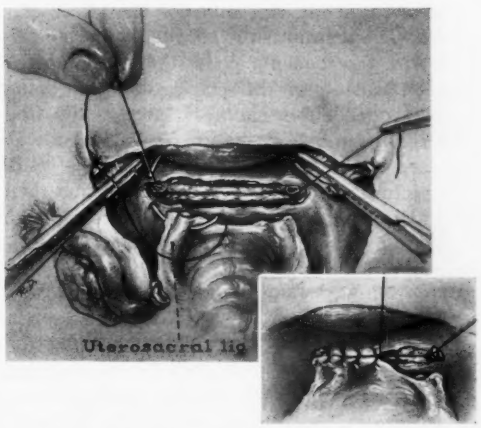


FIG. 9. Continuation of suture, shown in Figure 8, lower right, approximates vaginal vault to uterosacral and cardinal ligaments and pubocervical fascia. Inset, same suture continued to right, forming separate layer by suture of pubocervical fascia anteriorly and endopelvic fascia posteriorly.

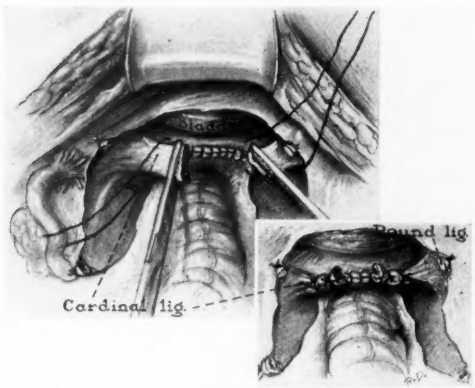


FIG. 10. Suturing of cardinal ligaments to vaginal angles and ligation of uterine artery beginning on right with pickup of peritoneum, uterosacral ligament, and corner of vaginal vault. Forceps on cardinal ligament and uterine vessels displaced medially while ligature is being tied. Position of ureter noted. Inset, Free second ligature on uterine vessels is optional.

pad is placed in the cul-de-sac, covering the two clamps that still remain on the cardinal ligament and uterine vessels. A sponge soaked in an antiseptic solution is inserted into the vagina.

Occasionally it is apparent at this stage that the patient has or is going to have inadequate support for the vaginal vault or that she has a potential or actual enterocele. To prevent prolapse of the vault, this situation should be corrected. The assistants retract the vagina anteriorly with the tenacula. With the left hand, the surgeon pulls up on the rectosigmoid, flattening out the deep cul-de-sac. The peritoneum and underlying endopelvic fascia are incised midway between the rectum and posterior vaginal wall. The rectum can be freed by first sharp and then finger dissection, with little or no bleeding from the posterior vaginal wall, for several centimeters, down to the level of the levator muscles.

The redundant cul-de-sac peritoneum is removed and a wedge is excised from the posterior vaginal wall (Fig. 8, left). The width of the wedge depends upon the need for preservation of vaginal function. The defect resulting is repaired with a continuous lock stitch of No. 0 chromic catgut placed from within the vagina and including the vaginal wall and rectovaginal fascia (Fig. 8, upper right). This procedure increases the stability of the posterior vaginal wall, narrows the vaginal apex, and brings the uterosacral and lateral supporting ligaments of the vagina toward the midline in front of the rectum. The uterosacral ligaments may be approximated with additional interrupted sutures. The vaginal vault is then closed.

The closure of the vaginal vault is effected by a continuous suture of atraumatic chromic No. 0 catgut. This is started at the right vaginal angle, the first stitch being so placed that when tied the small vessels in the angle of the vaginal vault are ligated (Fig. 8, lower right). The free end of the suture is left long and tagged with an instrument and is utilized for traction. The suture is continued toward the left, each bite being placed subcuticularly so that the squamous edges are everted into the vagina rather than buried. The suture does not enter the vagina and will not be exposed to contamination within it. Ligation of small vessels in the cuff should not be required, for the suture is sufficiently hemostatic. As the repair progresses from right to left, the tenacula are removed one at a time ahead of the suture line.

After the turn is made in the left vaginal angle and the last tenaculum is removed, the first assistant again elevates the vagina by opposing traction on the ends of the continuous suture which now emerge from both angles of the closed vaginal vault (Fig. 9). Staying medial to the left Ochsner forceps and hence medial to the ureter, the needle now picks up a generous portion of the left uterosacral ligament, turns anteriorly, and passes under the small vessels in the left vaginal angle and through the lateral supporting—cardinal—ligaments of the vagina and anteriorly picks up the layer of pubocervical fascia previously described (Fig. 9).

The suture is locked and then is returned across the vaginal vault, forming a separate layer by picking up the pubocervical fascia anteriorly and the peritoneum and endopelvic fascia posteriorly, or additional portions of the uterosacral ligaments if their approximation is considered advisable (Fig. 9, inset). To prevent strangulation and sloughing, this suture should not include those tissues approximated by the layer previously placed. When the right vaginal angle is reached, a secure bite is taken in the right uterosacral and the pubocervical fascia anteriorly. The suture is tied to the previously tagged end and then cut.

Thus a two layer closure of the vaginal vault is accomplished by a single continuous suture

which includes the pubocervical fascia anteriorly, the endopelvic fascia and uterosacral ligaments posteriorly, and part of the cardinal ligament—paracolpium—laterally for anatomic support. It should be emphasized that the vaginal vault has been elevated continuously from the depths of the pelvis, first by the tenacula and then by traction on the two ends of the suture. In such an easily visualized bloodless field it has been possible to note the position of the bladder, ureters, and rectum during each passage of the needle.

A straight forceps is placed on the vaginal vault for continued elevation to maintain this safe exposure. The upper portion of the right cardinal ligament, containing the uterine artery superiorly, is ligated and attached to the vaginal angle. To accomplish this the needle first enters the peritoneum, the uterosacral ligament, and the corner of vaginal vault below the tip of the clamp (Fig. 10). The forceps on the uterine vessels is pushed toward the midline by the first assistant, stretching the ligament and displacing the site of the planned tie medially from the ureter, the position of which again is noted. When tied, this suture not only ligates the uterine artery but also attaches the included portion of cardinal ligament to the angle of the new vaginal vault, restoring the continuity of the cardinal system, the upper pelvic diaphragm, which we consider to be the primary fascial support of the vaginal vault after hysterectomy, whether performed vaginally or abdominally. A second free ligature can be placed on the uterine vessels if the operator wishes. This process is repeated on the left (Fig. 10, insert).

About 1 centimeter medially from the suture fixing the cardinal ligament, another interrupted suture is placed in the vaginal vault. This is utilized to bring down the round ligament and fix it without tension (Fig. 11). This step is taken merely to facilitate peritonealization of the pelvis, not with the false hope that the round ligament, which is composed entirely of smooth muscle, will provide any significant support for the vaginal vault.

The pelvis is now peritonealized with a single continuous suture of No. 00 chromic catgut. This is started at the level of the right ovarian vessels in such a way that the vessels are again ligated and the stump extraperitonealized (Fig. 11). Once more, care must be exerted to avoid the nearby ureter when closing the peritoneum

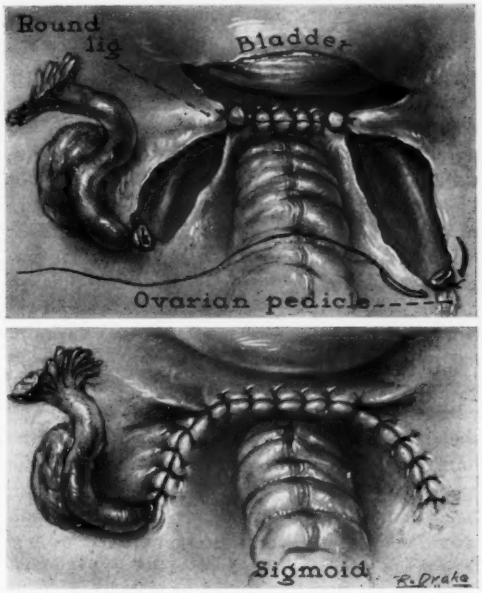


FIG. 11. Above, Suturing of round ligament to vaginal vault, which is also optional, to facilitate peritonealization. Below, Peritonealization of pelvis with single continuous suture that also provides second ligature upon ovarian vessels.

on each side wall of the pelvis. Identification of the structure before each passage of the needle into the medial leaf of the peritoneum is indispensable, as often the ureter is less than 1 centimeter from the peritoneal edge.

If present, the appendix should be removed after reperitonealization. The techniques for appendectomy and for closure of the abdominal incision require no elaboration.

COMMENT

The method presented for total abdominal hysterectomy varies considerably from many of those previously reported and from those we have had the privilege of observing elsewhere. We have no desire to represent the procedure described as greatly superior to the method used by many other experienced gynecologists; however, it is our impression that for the occasional operator—whether general practitioner, general surgeon, or gynecologist—this comparatively simple technique for hysterectomy is easily acquired and, of more importance, provides great safety at every step.

Emphasis has been placed on adequate exposure, a maxim of surgery regardless of the operative procedure but one that has been sadly neglected in relation to total abdominal hysterectomy. This requires not only a generous abdominal incision for visualization of the uterus, tubes, and ovaries but also ample room for identification of the ureters, constant exposure of the bladder base and rectum, and scope for safe closure of the vault with accurate visualization of the anterior and posterior vaginal walls. For those who cringe at the suggestion of routinely identifying or exposing the ureters throughout their course below the pelvic brim, it should be stated that this procedure can be accomplished without picking up, stripping, or traumatizing the structures in any way. However, when the nature of the pelvic disease dictates, or when the ureters appear to be dangerously close, they can be mobilized with much less risk of damage than would accrue from continued ignorance of their exact position.

Although the closure of the vaginal vault described is more meticulous and time-consuming than some methods previously reported, we believe that it obviates completely postoperative bleeding from the vaginal cuff, sloughing of the vaginal vault, and the occurrence of granulation in this region. Moreover, the subcuticular everting closure accurately approximates rather than buries the squamous edges of the vaginal walls so that rapid healing may occur. Regardless of this aspect of the technique, the most important feature of the vaginal closure consists of the constant elevation of the vaginal cuff from the pelvic depths, first by tenacula and subsequently by traction on the sutures used for closure. Thus the reconstruction can be undertaken in the presence of good lighting with direct visualization of the bladder base, rectum, and vaginal edges and in a relatively dry field.

As we have previously reported, prolapse of the vaginal vault after hysterectomy is not peculiar to the vaginal operation. We continue to see many referred patients in whom prolapse has developed within a few months after abdominal hysterectomy. Besides errors of surgical judgment, for instance, abdominal hysterectomy for uterovaginal prolapse, the errors of technique that seem to be largely responsible for postoperative prolapse of the vaginal vault are dependence upon only the uterosacral and round ligaments for vaginal support, failure to reattach the cardinal ligament securely to the lateral vaginal vault, and neglect of potential or actual cul-de-sac hernia.

In our experience, which consists of 400 to 500 abdominal hysterectomies annually, the present technique provides excellent and permanent support for the vaginal vault, especially when potential or actual enteroceles are noted and managed by the method described. Obviously, no operative technique can be expected to compensate for a gross error in surgical judgment, such as the attempt to correct extensive uterine prolapse and relaxation of the vaginal wall by utilization of the abdominal route alone.

THE SURGEON'S LIBRARY

Reviews of New Books

Henry Stanley Plummer; a Diversified Genius. By FREDRICK A. WILLIUS, M.D., M.S.(in Med.). 70 pages, illustrated. $4.50. Springfield, Ill.: Charles C Thomas, 1961.

Reviewed by SUMNER L. KOCH

THE NAME of Henry Plummer will live in medical annals both because of his contributions to the treatment of hyperthyroidism and to the growth and development of the Mayo Clinic. His early ambition was to enter the field of engineering, but although he followed in the footsteps of his father and grandfather to become a physician, he brought to his profession an especial interest in everything which physical science could contribute to medicine. The x-ray, the electrocardiograph and, later, laboratory methods for determining the basal metabolism, all were "grist for his mill," and under his direction and guidance were brought at an early stage in their development to the service of the patients in whom he was so vitally interested.

In 1906, when he was only 2 years out of medical school, he demonstrated to Dr. W. J. Mayo, who had been called into consultation by the senior Dr. Plummer, the blood picture of a patient with aleukemic leukemia. This demonstration under the microscope so impressed Dr. Mayo that Henry Plummer was invited to join the staff at Rochester, and so began an association that lasted until his death.

His interest in thyroid disease, aroused by his observation of one of his father's cases even before he entered medical school, was stimulated by the large number of goiter patients that came to the Clinic. The seriousness of the problem, particularly in patients suffering with exophthalmic goiter, the grave risks associated with surgical treatment, the discovery of thyroxin in 1910 by Kendall at the Mayo Clinic, and its importance to the understanding of the function of the thyroid gland now are a part of well known medical history.

The evolution of the basal metabolism laboratory under Boothby and Plummer was another forward step in the exact evaluation of thyroid function. Finally, in 1923, Plummer's conclusions that the excessive secretion of thyroxin in the hyperplastic thyroid gland was deficient in iodine led to the administration of iodine before thyroidectomy in patients with exophthalmic goiter. How this treatment affected the patient critically ill from an intense toxemia, and how completely the picture was changed are also well known. The author says, and without exaggeration, "... this important contribution without a doubt saved the lives of countless patients."

Probably less well known than Plummer's medical contributions, and the important part he played in the organization and establishment of the Mayo Foundation for Medical Education and Research, the Graduate School of the University of Minnesota, is the active role he played in the physical development of the Mayo Clinic. In 1910, when it became necessary to provide larger quarters to care for the constantly increasing number of patients, a building committee consisting of Mr. Harry Harwick, Dr. Louis Wilson, and Dr. Plummer was appointed to design a building which would provide the needed facilities. In Harwick's words, "After a few weeks there was really only one member: Dr. Plummer."

The 1914 Mayo Clinic building, containing many unique features which were "essentially Dr. Plummer's work," was only a beginning. In the mid 1920's it was no longer adequate, and plans were made to construct a building which would meet the needs of the Clinic for the foreseeable future. "In the planning of the new building Henry Plummer immediately became the hub around which all activity centered. During the three years of its construction we saw little of him except for occasional glimpses, carrying large rolls of blue prints under his arms."

Interestingly, the first step in the new building program was the planning and construction of a modern power and heating plant. Only when this was completed, with provisions for using natural gas, coal, or fuel oil, and when an independent supply of water was assured, did the construction of the new 16 story building, now known as the Plummer Building, proceed.

Two details of many that illustrate the engineering skill and ingenuity that characterized this physician-engineer are particularly intriguing. To make sure that elevator service would be adequate and efficient he visited mercantile establishments in various cities, where "rush hours" were comparable to those in the Clinic, to help determine how many units would be needed in the new building. After discussing the problem with representatives of the manufacturer "the chief engineer remarked that Henry Plummer knew more about elevators than he did."

In order to facilitate the work of the secretaries in assigning patients to consulting rooms and to enable "roving consultants" to see at a glance where their services were needed Dr. Plummer designed an intricate electrical system with colored lights above the doors of the examining rooms, and corresponding lights at the central desk on each floor. When the engineer of one of the leading manufacturers of electrical equipment told him the plan was not feasible Dr. Plummer handed him blueprints of the system which he had correctly worked out to the last detail.

Dr. Plummer died on December 31, 1936. One would wish that he could have lived to see the construction of the newest addition to the Clinic buildings. One cannot doubt that the 1953 building contains many of the "Plummer ideas" that helped to make its predecessors outstanding examples of efficiency and architectural beauty.

We are indebted to Dr. Willius for a graphic picture of the life and contributions of the man whom he has well named, "A Diversified Genius."

Traumatic Lesions of Peripheral Vessels. By CARL W. HUGHES, A.B., M.D., and WARNER F. BOWERS, A.B., B.Sc., M.D., M.S., Ph.D. 191 pages, 58 illustrations. $8.00. Springfield, Ill.: Charles C Thomas, 1961.

Reviewed by F. A. SIMEONE

THE STATED OBJECTIVE of the authors of this book is "to present the detailed surgical care of traumatic lesions of peripheral vessels." This they achieved by drawing upon their extensive experience with the wounds of the blood vessels encountered during World War II and, especially, in the Korean conflict. The feasibility and advantages of restoring continuity to injured vessels, tried sporadically before and during World War II, were demonstrated in the Korean experience. The authors played an important part in this demonstration.

The book consists of 8 chapters; the first 3 provide historical and experimental background. In the interest of brevity, this information has been presented rather sketchily and almost in outline form. The reader would have welcomed additional interpretation and comment on the significance of the several developments in vascular surgery.

Chapters IV through VII are the best in the book. They deal with very practical matters concerned with the management of both immediate and chronic lesions of the arteries and veins. The authors describe in detail the many points which can determine success or failure. Perhaps the experienced "vascular surgeon" may not find much that is new in these chapters, but the surgical resident and the surgeon who only occasionally encounters traumatic vascular problems in his practice will find them very useful. In the final chapter, the surgical anatomic approaches to the peripheral arteries are described with helpful suggestions.

Each chapter has an excellent bibliography in which can be found references to reports of results of the advocated form of therapy for individual arteries used during the Korean action. Again, in the interest of brevity, these are not tabulated. There are numerous illustrations, but, unfortunately, in many, detail has been lost in reproduction and, therefore, they mean more to the writer than to the reader.

The experienced vascular surgeon will find very little cause for disagreement with the contents. Some will object to the implication that arteriography with the usual radio-opaque media can cause serious "spasm," or to the use of the word "graft" for the insertion of materials which are not expected to live. Some statements may have little objective evidence to support them, such as the statement that when arteries are to be ligated they should not be ligated in continuity because this "supposedly tends to potentiate spasm in the arterial tree and gives a more painful limb." In their discussion of the management of closed injuries, the authors recommend blocking the vasoconstrictor fibers to the limb by means other than sympathectomy. While this may decrease the vascular resistance in the collateral arterial bed and thereby seemingly relieve the "spasm," relaxation of the spastic artery should not be expected. The vessel should be explored without undue delay when adequacy of the circulation is in question.

The critical reader will find editorial fault with the publication since there are numerous typographic errors, such as "facial" for fascial (p. 66), "subcutaneaous" (p. 92), "hemolytis" (p. 130), "sternomastiod" (p. 180), and profunda "femoral" for profunda "femoris" (p. 130). Here and there, grammatical construction could have been revised.

While these editorial matters do condition readability, the fact remains that the authors have assembled a great deal of very useful information.

Neoplastic Disease at Various Sites; Cancer of the Rectum. Edited by CUTHBERT E. DUKES, O.B.E., M.D., M.Sc., F.R.C.S. Vol. III. 295 pages, 82 illustrations. $10.00. Baltimore: The Williams & Wilkins Co., 1960.

Reviewed by ROBERT TURELL

MOST OF THE CONTRIBUTORS of this book are well known British intestinal surgeons and/or pathologists. In spite of the apparent lack of up-to-dateness, the vast subject of cancer of the rectum is well covered, though somewhat too statistically.

In the short discussion of the etiology, Dukes reiterates that very little is known of the cause of human rectal cancer and that this lesion is rare in animals living under natural conditions. Colonic neoplasms in mammals other than man are discussed thoroughly by Roberts. The pathology of rectal cancer is comprehensively discussed by the editor who has had great experience with colonic neoplasms at the St. Mark's Hospital, London, England. He alludes to his famous and sensible prognostic classification restating that the crude 5 year survival rate was 81.2 per cent for class A cases; 64 per cent for class B cases, and only 27.4 per cent for class C cases. After making due allowance for intercurrent deaths during the 5 year period, his corrected survival rate was increased considerably. Dukes also uses these statistics in the chapter on therapeutic results to point out that in the immediate future the best hope for improvement in the

results of surgical treatment of rectal cancer lies in earlier diagnosis and the earlier institution of operative therapy.

Morson, in the discussion of epidermoid cancer in the anal region distinguishes between the nature of this neoplasm occurring in the perianus and that in the anal canal. The former is believed to offer a better prognosis because it produces more keratin in contradistinction to the anal tumor which is usually a poorly differentiating nonkeratinizing squamous cell cancer.

There is reason to believe that these points are not universally appreciated. At this time, it may be preferable to subdivide the A cases into A′ class for tumors which are limited to the mucous membrane only without invasion of the muscularis mucosae. The prognosis in the A′ cases is excellent no matter how simple the treatment. The prognosis of squamous cell cancer in the perianus appears to be influenced not only by the keratin distribution as stated by Morson but also by other, still unknown, biologic factors, and possibly by the earlier recognition and earlier effective, albeit simple, treatment.

Goligher's chapter on the choice of operation is superb and succinct as is the one by Parks on the anatomic and physiologic considerations in relation to operations for rectal cancer. The common operative procedures are described individually by Abel, Gabriel, Lloyd-Davies, and Morgan. Unfortunately, the techniques are not illustrated. The section on postoperative care and complications was extremely well handled by the respective authors.

It is to be hoped that the subsequent edition of this superb work will contain: a fuller discussion of the cancer potential of chronic ulcerative colitis and adenomatous polyps; illustrations of the operative technique since, according to the Chinese proverb, one picture is worth more than 10,000 words; and a more extensive dissertation on the treatment of the malignant adenoma.

Everyone interested in diseases of the intestinal tract will profit enormously by reading this book.

Enzymes in Clinical Medicine. By IRVING INNERFIELD, M.D. 334 pages, illustrated. $11.95. New York, Toronto, and London: McGraw-Hill Book Co., Inc., 1960.

Reviewed by EUGENE E. CLIFFTON

THE AUTHOR of this volume, Irving Innerfield, is a pioneer in the study of proteolytic enzymes in thrombolysis and as anti-inflammatory agents in the treatment of inflammation. Unfortunately, the text is devoted almost entirely to the effects of these materials, primarily trypsin and varidase, upon thrombophlebitis and traumatic and inflammatory lesions. Data supporting the use of these materials are complete although much of the evidence against their use or their effectiveness has not been given and very little information reported upon the many other enzymes which are, or may be, of importance in clinical medicine in the near future. There is a great need for a comprehensive work on this subject but this volume does not fill that need. It contains a strange mixture of empiricism and scientific viewpoints and sometimes it is difficult to distinguish one from the other. For instance, it is a well established fact that trypsin activates plasminogen, the human proenzyme, but it is not clearly stated that this activation is minimal. Secondly, it may be assumed from the work of Astrup and others that saliva contains plasminogen, but there is no real evidence that activation of this plasminogen in the saliva by buccal varidase is significant or has an effect in the blood. Indeed, the amounts of the enzyme contained in the buccal tablet are much smaller than those used intravenously without evidence of activation of plasminogen to plasmin.

The chapter on proteolytic enzymes and inflammation contains interesting suggestions on the mechanisms of fibrin formation and microblockade as a factor in inflammatory disease. The effect of proteases on this fibrin and microblockade is not integrated sufficiently which does not lead to a better understanding of this mechanism or the effects of enzymes upon the inflammation. The concept that trypsin and varidase act by activation of plasminogen has never been supported by any objective evidence.

The chapter on enzyme inhibitors is well written but, unfortunately, there are very few supporting data or supporting references for the evidence presented.

Congenital Malformations of the Heart. By HELEN B. TAUSSIG, M.D. 2nd ed. Vol. I: **General Considerations.** 204 pages, illustrated. $4.75. Vol. II: **Specific Malformations.** 1049 pages, illustrated. $17.50. Cambridge, Mass.: Harvard University Press, 1960.

Reviewed by H. WILLIAM SCOTT, JR.

THE EXTENSIVE ADVANCES in the understanding, diagnosis, and treatment of cardiac anomalies which have been made in the last 15 years are reflected in the second edition of Taussig's *Congenital Malformations of the Heart*. The author has presented the material in two volumes in this revised edition.

Volume I has 204 pages and deals with general considerations of the embryology, etiology, basic principles of diagnosis, methods of evaluation, and clinical management of congenital cardiac defects. This part of the work is designed predominantly as an introduction to the subject of congenital heart disease for the student and the practitioner. The basic material is presented logically and concisely and there are numerous illustrations and diagrams which add to the clarification of the text. The viewpoint of the clinician is dominant throughout. The special diagnostic methods of angiocardiography, aortography, and cardiac catheterization are treated with simplicity, and their indications, contributions, and limitations in evaluation of cardiac anomalies are discussed lucidly.

Specific malformations are described in detail in the 1049 pages of volume II. The historical backgrounds, with appropriate references, and the present day diagnostic and therapeutic approaches to some 58 categories of congenital cardiovascular defects are presented. The various anatomic lesions are depicted by Leon Schlossberg's beautiful drawings, and their pathophysiologic effects and diagnostic aspects are illustrated by circulatory diagrams, electrocardio-

graphic tracings, roentgenograms, and angiocardiograms. The author's wealth of experience is liberally imparted in the detailed discussions of differential diagnosis, prognosis, and therapy.

The book is designed predominantly for the pediatrician, the internist, and the cardiologist. It is of great value for the surgeon interested in cardiovascular anomalies but provides disappointingly meager information concerning the surgical management of the malformations which are discussed.

Pathogenesis and Treatment of Cerebrovascular Disease. Edited by WILLIAM S. FIELDS. 556 pages, illustrated. $15.00. Springfield, Ill.: Charles C Thomas, 1961.

Reviewed by HUSHANG JAVID

THIS TIMELY BOOK entitled *Pathogenesis and Treatment of Cerebrovascular Disease*, covers the subject thoroughly and is of great interest to doctors in every field of medicine. Diagnosis and management of common cerebrovascular disorders are discussed, in addition to some unusual lesions which are a challenge to neurosurgeons and vascular surgeons. A group of 29 scientists and physicians contributed to its four major sections which are masterfully compiled and edited by William S. Fields. In the first section, anatomy of the vascular system of the brain is discussed with particular emphasis on embryology. The section on occlusive cerebrovascular lesions is effectively presented, and many aspects of the disease, such as pathogenesis, diagnosis, and medical and surgical management are discussed. In reading this portion, one learns much from the discussion by the various participants, and I recommend it highly. The other two parts concern intracerebral hemorrhage, subarachnoid hemorrhage, and intracranial saccular aneurysms. The management of these lesions is fully covered, including the use of carotid occlusion, intracranial surgical procedures, hypotension, and hypothermia.

This edition is scholarly and stimulating since controversial viewpoints are presented in the discussion of various chapters.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

RECURRENT DISLOCATION OF THE SHOULDER. By H. F. Moseley, D.M., M.Ch.(Oxon.), F.R.C.S.(Eng. and Can.), F.A.C.S. 156 pages, 93 illustrations, 35 stereoscopic color illustrations. $13.50. Montreal: McGill University Press, 1961.

PROGRESS IN MEDICAL GENETICS. Edited by Arthur G. Steinberg, Ph.D. Vol. I. 334 pages, illustrated. $9.75. New York and London: Grune & Stratton, 1961.

THE ADRENAL CORTEX. By 19 authors. Edited by Henry D. Moon, M.D. 296 pages, illustrated. $10.50. New York: Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, 1961.

PATHOLOGY OF TUMOURS. By R. A. Willia, D.Sc., M.D., F.R.C.P. 3rd ed. 1002 pages, 500 illustrations. $21.00. Washington, D. C.: Butterworths, 1960.

ESSENTIALS OF NEUROSURGERY FOR STUDENTS AND PRACTITIONERS. By Sean Mullan, M.D. 258 pages, 87 illustrations. $6.75. New York: Springer Publishing Co., Inc., 1961.

PRINCIPLES AND TECHNICS OF REHABILITATION NURSING. By Florence Jones Terry, B.A., R.N., P.T., O.T., Gladys S. Benz, R.N., M.A., Dorothy Mereness, R.N., A.B., M.N., Ed.D., and Frank R. Kleffner, Ph.D. Edited by Deborah MacLurg Jensen, R.N., M.A. 2nd ed. 338 pages, 42 illustrations. $6.00. St. Louis: The C. V. Mosby Co., 1961.

YOU AND YOUR DOCTOR; THE COMMON SENSE GUIDE TO MEDICAL CARE. By William H. Potter, M.D. 275 pages, no illustrations. $5.00. New York: Duell, Sloan & Pearce, Inc., 1961.

PHLEBOGRAPHY AND VENOUS PRESSURE DETERMINATION; A STUDY INTO THE CORRELATION OF THE DATA GAINED FROM THESE METHODS. By M. N. Van der Heyde, M.D. 83 pages, illustrated. $5.00. Springfield, Ill.: Charles C Thomas, 1961.

STANDARD NOMENCLATURE OF DISEASES AND OPERATIONS. Edited by Edward T. Thompson, M.D., F.A.C.H.A., and Adaline C. Hayden, C.R.L. 5th ed. 964 pages, no illustrations. $10.50. New York, Toronto, and London: The Blakiston Division, McGraw-Hill Book Co., Inc., 1961.

HYPNOSIS IN OBSTETRICS; OBSTETRIC HYPNOANESTHESIA. By Ralph V. August, M.D., F.A.C.O.G., F.I.C.S. 153 pages, 4 illustrations. $10.00. New York, Toronto, London: The Blakiston Division, McGraw-Hill Book Co., Inc., 1961.

OBSTETRICAL EMERGENCIES. By Denis Cavanagh, M.B., Ch.B.(Glasgow), F.A.C.O.G. 353 pages, 73 illustrations. $12.50. Springfield, Ill.: Charles C Thomas, 1961.

AMERICAN COLLEGE OF SURGEONS

I. S. RAVDIN, Philadelphia, *President*

ROBERT M. ZOLLINGER, Columbus, Ohio, *President-Elect*

PRELIMINARY PLANS FOR THE 47TH CLINICAL CONGRESS CONRAD HILTON HOTEL, CHICAGO, ILLINOIS 2 THROUGH 6 OCTOBER 1961

SECTIONS of the program of the 47th Clinical Congress have appeared in the three preceding issues of SURGERY, GYNECOLOGY & OBSTETRICS. In this issue, the daily schedule of the Forum on Fundamental Surgical Problems, television and film programs, and scientific exhibits are presented.

Since the first Forum in 1941, this part of the Clinical Congress program has developed until it is today a true forum before which young surgeons and research scientists from the United States and Canada can present the newest experimental studies in general surgery and the surgical specialties. There will be 22 sessions, scheduled morning and afternoon, Monday through Thursday, with a total of 258 papers. These concise reports of new contributions have made the Surgical Forum an important factor in surgical progress by stimulating an inquiring, investigative atmosphere in medical schools and hospitals within the two countries.

The following members of the Forum Committee have planned an interesting program for this year: William P. Longmire, Jr., Chairman, William H. Muller, Jr., Vice-Chairman, Oscar Creech, Jr., Clarence Dennis, William J. Grove, C. Rollins Hanlon, J. William Hillman, William D. Holden, Hugh J. Jewett, Milton L. McCall, Somers H. Sturgis, Joseph E. Murray, William H. Sweet, and Edward R. Woodward.

Fellows whose dues are paid to 31 December 1960 pay no registration fee; for those whose dues are not paid as of this date the fee is $40.00. Non-Fellows pay $40.00. For members of the Federal Services (full-time) the fee is $20.00. No registration fee is charged Initiates, members of the Candidate Group, and surgical residents. The resident should provide a note of identification signed by his chief of surgery or hospital administrator. Everyone attending a Postgraduate Course pays a fee of $10.00. To expedite registration, it is requested that everyone carry medical identification. Official registration forms are available from the American College of Surgeons headquarters, 40 East Erie Street, Chicago 11, Illinois.

Wives are cordially invited to attend. The Ladies Entertainment Committee, under the chairmanship of Mrs. Paul H. Holinger, promises a week of interest and fun.

Forum on Fundamental Surgical Problems

Monday, 8:30 a.m.—12:00 noon

CANCER

Demonstration of Serum Fractions Influencing Cell Growth. EDWARD D. MCLAUGHLIN, Bethesda.

Humoral Accelerating Effect of Regenerating Liver on Distant Tumor Take and Growth in Rats. FREDERIC A. DE PEYSTER, E. A. JOBGEN, and M. A. PETRAVICIUS, Chicago.

Time Survival Studies of Circulating Cancer Cells. ROBERT E. MADDEN, New York.

Spillage and Recurrence of Colonic Carcinoma. ISIDORE COHN, JR., EFRAIM A. GONZALEZ, JR., and MOHAMMAD ATIK, New Orleans.

On the Carcinogenicity of Human Gallstones. JOSEPH G. FORTNER and HENRY T. RANDALL, New York.

Microcirculatory Study of the Dynamics of Metastasis. JOHN F. POTTER, EDWARD F. ROONEY, and LEON I. BLOCK, Washington.

Viruses and Cancer: Studies of Human Leukemia. JAMES T. GRACE, JR., STEPHEN J. MILLIAN, EDWIN A. MIRAND, and R. S. METZGAR, Buffalo.

Morphology of Viruses Isolated from Human Leukemic Tissue. GUY OWENS, STEPHEN J. MILLIAN, EDWIN A. MIRAND, and JAMES T. GRACE, JR., Buffalo.

Heterologous Transplantation of Tissue-Cultured Human Tumor Cells into Laboratory Animals. AKIHIKO KOIKE and GEORGE E. MOORE, Buffalo.

Host Conditioning for Homologous Tumor Transplants. GEORGE C. HENEGAR, ELIZABETH J. JACKSON, and FREDERICK W. PRESTON, Chicago.

Survival of Skin Homografts in Terminal Cancer Patients. ROBERT J. GARDNER, JOHN T. HART, WARREN R. SUTTON, and FREDERICK W. PRESTON, Chicago.

Adrenal Steroid Metabolism in Patients with Bronchogenic Carcinoma. ALAN C. HYMES and RICHARD DOE, Minneapolis.

Monday, 8:30 a.m.—12:00 noon

METABOLIC ALTERATIONS WITH EXTRACORPOREAL CIRCULATION

Digitalis Tolerance in Dogs Following Extracorporeal Circulation. RAYMOND W. BROWNING, MASAUKI HARA, BEN M. LINCOLN, DOYNE WILLIAMS, WILLIAM T. DUNGAN, and JOHNSON BAKER, Little Rock.

Digitalis Tolerance Following Extracorporeal Circulation. ROBERT R. MAGINN, VALLEE L. WILLMAN, THEODORE COOPER, and C. ROLLINS HANLON, St. Louis.

Effect of Cardiopulmonary Bypass on Myocardial Digoxin Concentration. PAUL A. EBERT, LAZAR J. GREENFIELD, W. GERALD AUSTEN, and ANDREW G. MORROW, Bethesda.

Comparison of the Effects of Membrane and Nonmembrane Oxygenators on the Biochemical and Biophysical Characteristics of Blood. W. H. LEE, JR., D. KRUMHAAR, G. DERRY, DAVID SACHS, S. H. LAWRENCE, GEORGE H. A. CLOWES, JR., and JAMES V. MALONEY, JR., Los Angeles.

Hemostatic Defects in Patients Undergoing Cardiac Bypass. HENRY GANS and WILLIAM KRIVIT, Minneapolis.

Vasoactive Substances Liberated by Prolonged Bubble Oxygenation. MARTIN HOLLENBERG, ROBERT PRUETT, Minneapolis, and ALAN P. THAL, Detroit.

Experimental Studies of Myocardial Metabolism and Contractile Force of the Homotransplanted Heart. PETER HAIRSTON and WILLIAM H. MULLER, JR., Charlottesville.

An Experimental Evaluation of Techniques for Maintaining the Heart During Prolonged Aortic Occlusion. W. GERALD AUSTEN, PAUL A. EBERT, LAZAR J. GREENFIELD, and ANDREW G. MORROW, Bethesda.

Liver Metabolism During Extracorporeal Bypass. JAY L. ANKENEY, HENRY DIMLICH, CLYDE LESTER NASH, and THOMAS CARTER, Cleveland.

Effects of Tromethamine (TRIS) on Myocardial Activity and Metabolism. TAKASHI TANAKA, BRUCE C. PATON, and HENRY SWAN, Denver.

Effects of a Dialyzer During Total Cardiac Bypass. VITO V. PAGANO and TERUO HIROSE, New York.

Long Term Extracorporeal Circulation in the Development of an Artificial Placenta for Respiratory Distress of the Newborn. JOHN C. CALLAGHAN and JOSE DELOS ANGELES, Edmonton.

Monday, 8:30 a.m.—12:00 noon

PHYSIOLOGY OF GASTRIC SECRETION

Effect of the Antral Inhibitory Hormone on Phases of Gastric Secretion. JAMES C. THOMPSON and HARVEY J. LERNER, Philadelphia.

Gastric Secretion and Antrum *p*H; a Correlation Using in Situ Measurements. DAVID WILLIAM FOERSTER and MERLIN K. DUVAL, JR., Oklahoma City.

Mechanism of Antrum Acid Inhibition. ALSTRUP N. JOHNSON, JR., HARRY A. OVERHELMAN, JR., EDWIN EIGENBRODT, and G. ROBERT MASON, Palo Alto.

Effect of Cortisone on the Antral Phase of Gastric Secretion. DEMETRE M. NICOLOFF, NELSON H. STONE, ARNOLD S. LEONARD, EDWARD T. PETER, and OWEN H. WANGENSTEEN, Minneapolis.

Effect of Hepatocellular Injury on Gastric Secretion in Dogs. JOHN J. SKILLMAN, WILLIAM SILEN, HAROLD A. HARPER, JAMES C. NEELY, and E. LEE SIMMONS, San Francisco.

Effect of Portacaval Transposition on the Early Intestinal Phase of Gastric Secretion. JOHN M. SOUTHWELL, DAVID M. BAKER, R. BRUCE WINNER, and JAMES S. CLARKE, Los Angeles.

Effect of Ethionine on Gastric Secretion. DAVID A. TAFT, DANIEL W. ELLIOTT, J. M. B. BLOODWORTH, and ROBERT M. ZOLLINGER, Columbus, Ohio.

Effect of Parenteral Alcohol on Gastric Secretion. REINOLD E. WEISE, HERBERT SHAPIRO, and EDWARD R. WOODWARD, Gainesville.

Effect of Hypothalamic Stimulation on Gastric Secretion and Adrenal Function in the Dog. CHARLES F. ZUKOSKI, HENRY M. LEE, and DAVID M. HUME, Richmond.

Gastric Response to Induced Hyperparathyroidism. JAMES E. ALLEN and DANIEL W. ELLIOTT, Columbus, Ohio.

Role of Potassium in Histamine Stimulated Gastric Pouch Juice. HELENA GILDER, FRANK G. MOODY, and JOHN M. BEAL, New York.

Effects of Acetazolamide (Diamox) and of Metabolic Acidosis and Alkalosis upon Gastric Acid Secretion in Dogs. FRANK M. BYERS, PAUL H. JORDAN, JR., and THOMAS H. MAREN, Gainesville.

Monday, 8:30 a.m—12:00 noon

ORTHOPEDIC SURGERY

A Study of the Influence of Heparin and Low Molecular Weight Dextran on Tourniquet Palsy. W. G. RHEA, JR., and JOHN H. FOSTER, Nashville.

Precise Measurement of the Extremities—Volumetric Technique with Results. MARCELINO CHAVEZ, GEORGE W. SMITH, and HAROLD ENGLER, Augusta, Georgia.

A Method for Analyzing Muscle Function in Locomotion. NEIL C. TAPPEN and JACK WICKSTROM, New Orleans.

Structural Changes Induced in Articular Cartilage of the Knees of Adult Rabbits by Sustained Pressure. W. O. SOUTHWICK and E. S. CRELIN, New Haven.

Recent Observations in the Therapy of Frostbite. PIETER DE JONG, MICHAEL R. GOLDING, PHILIP N. SAWYER, and SIGMUND A. WESOLOWSKI, Brooklyn.

Frostbite; a Method of Treatment Including Rapid Rewarming. WILLIAM J. MILLS, JR., Anchorage.

A Possible Substitute for the Preserved Bone Homograft. C. ANDREW L. BASSETT and DANIEL K. CREIGHTON, JR., New York.

Contribution of Various Sized Vessels to Postfracture Enlargement of the Vascular Bed. JAMES B. WRAY, Syracuse.

Metabolic Studies in Patients with Osteoporosis. GEORGE E. SPENCER, JR., WILLIAM E. ABBOTT, STANLEY LEVEY, and CHARLES H. HERNDON, Cleveland.

Pathologic Physiology of Pulmonary Fat Embolism; Mechanical and Chemical Alterations with an Effective Antidote. CHARLES E. YALE and LOUIS G. HERRMANN, Cincinnati.

Fat Embolism; Prophylactic Treatment with Lipase Inhibitors. FEDERICO ADLER, SING-PING LAI, and LEONARD F. PELTIER, Kansas City, Kansas.

Tetracycline Localization in Certain Neoplasms of Bone. ROBERT W. BAILEY and PAUL D. LEVIN, Ann Arbor.

Monday, 1:30—5:00 p.m.

REGIONAL AND ORGAN PERFUSION; GENERAL PROBLEMS

Analysis of Agents for Use in Isolated Perfusion. ROBERT K. AUSMAN, Buffalo, and J. BRADLEY AUST, Minneapolis.

Role of Lymphatic Drainage in the Systemic Leak During Isolated Visceral Perfusion. W. STEWART HIATT, DALE E. BRETT, and PAUL R. SCHLOERB, Kansas City, Kansas.

Effects of Nitrogen Mustard on the Liver, Administered by the Isolated Perfusion Technique. W. B. CHUNG, A. D. FORWARD, and D. A. BROWN, Vancouver.

Isolation Perfusion and Oxygen Saturation; the Effect on the Binding of P-32 Tagged Triethylene Thiophosphoramide. DAVID SACHS, JOYCE SHINER, ROBERT O. BAUER, and DONALD B. ROCHLIN, Los Angeles.

Effective Use of a New Alkylating Agent in Doses Lethal to Bone Marrow with Protection by Tourniquets of Marrow in the Extremities. LOUIS E. GOODMAN, ALBERT SCHILLING, STANLEY P. KRAMER, ADOLPH ULFOHN, STANLEY MILLER, SHELDON KRAVITZ, SAMUEL D. GABY, DANIEL BAKAL, BENJAMIN WITTEN, and ARNOLD M. SELIGMAN, Baltimore.

Successful Perfusion of the Canine Kidney in Vivo. CHARLES BAXTER and TOM SHIRES, Dallas.

Osmotic Cell Damage During Glycerol Perfusion of the Isolated Canine Kidney. ROBERT J. RIVERS, JR., BLAKE CADY, HENDRICK BARNER, LEWIS L. HAYNES, and ELTON WATKINS, JR., Chelsea, Massachusetts.

A Method for Measuring Small Quantities of Antidiuretic Substances in Biologic Fluids. EARL F. WOLFMAN, JR., and WILLIAM W. COON, Ann Arbor.

Continuous Analysis of Blood Nitrous Oxide Content. GILBERT O. SPENCER, JR., LELAND C. CLARK, JR., and CHAMP LYONS, Birmingham.

Changes in Plasma Serotonin Concentration in the Surgical Patient; Its Possible Significance. HRANT H. STONE, SUSUMU HORIGUCHI, CELESTE C. DONNELLY, and PAUL NEMIR, JR., Philadelphia.

Arteriography Utilizing Radiographic Magnification Techniques. TIMOTHY TAKARO, STEWART SCOTT, and WILLIAM H. SEWELL, Oteen, North Carolina.

A New Method of Parabiosis in Dogs Utilizing a Common Channel with Aortic Cross Circulation. MARC I. ROWE, DAVID E. MARTIN III, LAWRENCE TOSE, DONALD C. NABSETH, and RALPH A. DETERLING, JR., Boston.

Monday, 1:30—5:00 p. m.

EFFECTS OF HYPOTHERMIA IN VARIOUS ORGAN SYSTEMS

Alterations in Myocardial Metabolism Subsequent to Hypoxic and Hypothermic Cardiac Arrest. WILLIAM F. BERNARD, HANS F. SCHWARZ, GEORGE HUG, S. EDWIN CARROLL, and HUBERT JOKINS, Boston.

Cardiac Dynamics During Partial Bypass for Profound Hypothermia (4 Degrees C.). ROBERT J. WILDER, BENJAMIN F. RUSH, RONALD H. FISHBEIN, and MARK M. RAVITCH, Baltimore.

Metabolic Alterations of Individual Organs During Cardiopulmonary Bypass and Profound Hypothermia. ROBERT G. ELLISON, LOIS T. ELLISON, EDWIN L. BRACKNEY, and THOMAS Y. YEH, Augusta, Georgia.

Use of Glycerol and Chloroform in Heart Preservation by Freezing. PETER J. CONNAUGHTON and F. JOHN LEWIS, Chicago.

Circulatory Effects of Pulmonary Hypothermia. RONALD DEE, ROBERT H. GOETZ, M. ROHMAN, V. M. GOETZ, and DAVID STATE, New York.

The Plasma Volume Expanding Effect of Low Molecular Weight Dextran in the Hypothermic Dog. CHRISTOPHER T. DRAKE and F. JOHN LEWIS, Chicago.

Hypercapnia—a Means of Increasing Oxygen Availability During Hypothermic Perfusion. WILLIAM G. MALETTE, J. B. FITZGERALD, Lackland Air Force Base, and BEN EISEMAN, Lexington.

Effect of Inhaling Carbon Dioxide on Brain Cooling During Hypothermia. BENJAMIN BACHARACH, H. MARTIN SNYDER, and JOHN Y. TEMPLETON III, Philadelphia.

Hypothermia of the Spinal Cord by Perfusion Cooling of the Subarachnoid Space. MAURICE S. ALBIN, ROBERT J. WHITE, DAVID E. DONALD, COLLIN S. MACCARTY, and ALBERT FAULCONER, JR., Rochester, Minnesota.

The Maintenance by Cold Perfusion of the Viability of the Devascularized Canine Kidney. ALBERT J. MACKSOOD, D. EMERICK SZILAGYI, and ROGER F. SMITH, Detroit.

The Influence of Hypothermia on Myeloid Maturation. MOHAMAD J. RASTEGAR, ROBERT L. WEBB, and STANLEY W. JACOB, Portland, Oregon.

Tuesday, 8:30 a.m.—12:00 noon

PLASTIC SURGERY

Standardized Flame Burns in Mice; Fluid and Electrolyte Shifts and Effects of Cross-Transplantation of Normal and Burned Skin. RAMON S. DE JESUS, CHARLES L. FOX, JR., JOSE M. FERRER, JR., and GEORGE H. HUMPHREYS II, New York.

Evaluation of Local Therapy of Second Degree Burns. J. FOREMAN, I. H. SOKOLIC, and JOHN M. HOWARD, Philadelphia.

Energy Expenditure in Two Severely Burned Patients. ALVARO RABELO, RONALD G. CLARK, and JOHN M. KINNEY, Boston.

Effects of Local Hypothermia on Pedicle Flap Tissue—II, Hemodynamic Changes. JOHN D. DES PREZ and CLIFFORD L. KIEHN, Cleveland.

Effect of Hypothermia on Circulatory Responses in the Canine Hind Limb after Tourniquet Ischemia. SAMEER SHEHADI, F. X. PALETTA, and THEODORE COOPER, St. Louis.

Clinical Criteria for Evaluating First Set, Accelerated, and White Graft Rejection in Human Skin Homografts. DAVID C. MARSHALL, ELI A. FRIEDMAN, DONALD P. GOLDSTEIN, LAURENCE HENRY, and JOHN P. MERRILL, Boston.

Acquired Immunologic Tolerance Following Parabiosis in Adult Mice of Diverse Genetic Strains. MILTON T. EDGERTON and SANDRA C. MORREL, Baltimore.

Effect of Exchange Transfusion and Intravenous Lymph Injection in Newborn Dogs on Homologous Split Thickness Graft Takes. MAUNG M. THAN, GARY R. SAMPSON, CARLOS MARTINEZ, and KAREL B. ABSOLON, Minneapolis.

Some Studies on the Production and Polymerization of Collagen in Healing Wounds. ERLE E. PEACOCK, JR., Chapel Hill.

An Evaluation and Comparison of the Regeneration and Healing Mechanism of Irradiated Homografts, Autografts, and Homografts in Avian Digital Flexor Tendons. FRANKLIN L. ASHLEY, LEONARD MARMOR, TEODOR POLAK, and ROBERT S. STONE, Los Angeles.

Surgical Removal and Replacement of the Mandibular Condyle in the Immature Pig. BYRON E. GREEN and JAMES H. HENDRIX, JR., Jackson.

Correction of Cerebral Hypotension After Ligation of the Carotid Artery; Experimental Study in Rabbits. ELDON R. DYKES and ROBIN ANDERSON, Cleveland.

Use of Autogenous Dermis for Protection of the Carotid Artery and Pharyngeal Suture Lines in Radical Head and Neck Surgery. PHILIP F. CORSO and FRANK P. GEROLD, New York.

Tuesday, 8:30 a.m.—12:00 noon

INFECTION; COAGULATION OF BLOOD

Studies of Pseudomonas Infections by a New Bacteriophage Typing Technique. JAMES B. GROGAN and CURTIS P. ARTZ, Jackson.

Protective Mechanism of Hypothermia in Experimental Infection. ROGER S. WOTKYNS, HIDEO HIROSE, Denver, and BEN EISEMAN, Lexington.

An Investigation of the Use of Radioactive Substances for the Detection of Infection. S. FRANK REDO, WILLIAM A. BARNES, and JEFFREY WENIG, New York.

Changes in Estimated Hepatic Blood Flow with Nonshocking Doses of Staphylococcus Toxin. RODNEY H. HERR, RICHARD G. SANDERSON, JOHN C. BIGELOW, JAMES O. SLAMA, and R. MARK VETTO, Portland, Oregon.

Regeneration of Skin Flora Under Normal Conditions. RALPH C. RICHARDS and PHILIP B. PRICE, Salt Lake City.

Mortality, After Severe Experimental Burns, of Rats Treated with Chloromycetin and with Sera of Rats Convalescing from Burns or from Open Wounds. OLE J. MALM and GEORGE J. M. SLAWIKOWSKY, Washington.

A Microradiographic Study of Developing Staphylococcal Inflammation Using Ultrasoft Roentgen Rays. JOHN FRANCIS BURKE and ULF FRIBERG, Boston.

Relationship of Operating Room Carriers of Staphylococcus Aureus to Wound Infections. DAVID D. B. WOO, THOMAS F. SILVA, JR., ALICE T. MARSTON, and CHESTER W. HOWE, Boston.

Effect of Fibrinolytic Agents on Blood Clot Pulmonary Emboli in Dogs. JOHN M. CAHILL and JOHN J. BYRNE, Boston.

Successful Application of an Assay Indicating Thrombolytic Activity in Excess of Plasma Inhibitors. MICHAEL HUME, New Haven.

Prevention of Thrombosis with the Use of a Negative Electric Current. SEYMOUR I. SCHWARTZ and JOHN W. RICHARDSON, Rochester, New York.

Production of Acute Nephrosis by Incompatible (Heterologous) Blood Transfusion and the Protective Effect of Low Molecular Weight Dextran. MOHAMMAD ATIK and R. GUTIERREZ-SAENZ, New Orleans.

Tuesday, 8:30 a.m.—12:00 noon

POSTGASTRECTOMY SYNDROME; LARGE AND SMALL INTESTINES

Effect of Intraluminal Hypertonic Glucose on Thoracic Duct Lymph. WALTON K. T. SHIM and THEODORE DRAPANAS, Buffalo.

Indirect Measurement of Intraluminal Volume Changes and Absorption Rates in the Small Intestine. RAY CRAMPTON, J. WILLIAM POPPELL, PARKER VANAMEE, and WALTER LAWRENCE, JR., New York.

Evidence for a Humoral Etiology of the Dumping Syndrome. LLOYD P. JOHNSON and JOHN E. JESSEPH, Seattle.

Effect of a Reversed Jejunal Segment upon Gastric Emptying, Nutrition, and Plasma Volume Following Subtotal Gastrectomy. RICHARD K. WILLMS, ROBERT T. ANGEL, and GEORGE L. JORDAN, JR., Houston.

Influence of Proximal Colostomy on the Size of Distal Colon Anastomosis in Dogs. HARRY L. BAILEY, J. KENNETH JACOBS, HAROLD A. COLLINS, and JOHN H. FOSTER, Nashville.

The Red Blood Cell; an Essential Element in Lethal Strangulating Obstruction of the Intestine. JOHN H. DAVIS and A. B. YULL, Cleveland.

Effects of Acute and Chronic Constriction of the Celiac Axis in the Dog. DONALD C. SPENCER and JOHN R. DERRICK, Galveston.

A New Method for the Diagnosis of Chronic Insufficiency of the Superior Mesenteric Artery. FRANK E. GUMP, ROBERT L. BEALS, and DAVID V. HABIF, New York.

Influence of Low Molecular Weight Dextran on Acute Occlusion of the Mesenteric Vein. DERWARD LEPLEY, JR., CARL J. MANI, and EDWIN H. ELLISON, Milwaukee.

The Use of Serotonin Antagonists in the Treatment of the Malignant Carcinoid Syndrome. WILLIAM T. WEAVER, EARL N. METZ, WILLIAM G. ANLYAN, and WAYNE R. RUNDLES, Durham.

The Rapid Degradation of 5-Hydroxytryptamine (Serotonin); Significance in the Carcinoid Syndrome. LEROY L. JOHNSON, GERALD W. PESKIN, and DOROTHY J. SENESKY, Philadelphia.

Anatomic and Functional Changes Resulting from Autotransplantation of the Canine Small Intestine. M. G. CHRISTY, W. B. ASHBY, P. K. BERG, G. E. APONTE, R. R. GREENING, and WALTER F. BALLINGER II, Philadelphia.

Tuesday, 1:30—5:00 p.m.

PHYSIOLOGY OF THE PANCREAS

Serum Insulin-Like Activity in the Pancreatectomized Dog. RICHARD H. EGDAHL and HAROLD L. GOLDBERG, Richmond.

Serotonin and Pancreatic Secretion. JOHN J. HUDOCK, ARCHIE KHENTIGAN, RAY CRAMPTON, PARKER VANAMEE, and WALTER LAWRENCE, JR., New York.

Influence of Body Temperature Variations on Pancreatic Function. P. N. SYMBAS, BENJAMIN F. BYRD, JR., J. S. JOHNSON, RACHEL YOUNGER, and JOHN H. FOSTER, Nashville.

Effect of Narcotic Analgesics on Pancreatic Secretion. PAUL J. M. HEALEY and JOHN J. BYRNE, Boston.

Retardation of the Progress of Experimental Pancreatitis with Trypsin Inhibitors. RUSSELL H. CANNON and M. D. TURNER, Jackson.

Study of the Effect of Trypsin Inhibitor in Acute Hemorrhagic Pancreatitis in Dogs. SAMUEL RIBACOFF, ALFRED HURWITZ, RENE KHAFIF, and FELIX SIEGMAN, Brooklyn.

Calcium Excretion by the Pancreas in Hypercalcemia. RICHARD C. MCPHERSON and WILLIAM G. PACE, Columbus, Ohio.

Electrophoretic Patterns of Serum Leucine Aminopeptidase in Patients with Pancreatic and Hepatobiliary Disease. ALEXANDER M. RUTENBURG, EDGAR E. SMITH, and ESTEBAN P. PINEDA, Boston.

Lipotropic Effect of Vitamin B-12 and Folic Acid in Depancreatized Dogs. EDWARD PALOYAN and PAUL V. HARPER, JR., Chicago.

Pancreatic Response to Alcohol Following Antral-Esophagostomy. ARNOLD M. EPSTEIN and ROGER D. WILLIAMS II, Columbus, Ohio.

Absorption of Labeled Triolein as a Diagnostic Aid in Obstructive Jaundice. MYRON ARLEN and JEROME ADESMAN, Brooklyn.

Malignant Obstructive Jaundice as Detected by Levels of Rose Bengal in the Blood After 24 Hours. NORMAN B. ACKERMAN and ARTHUR S. MCFEE, Minneapolis.

Tuesday, 1:30—5:00 p.m.

FACTORS INFLUENCING THE CORONARY CIRCULATION

Blood Supply to Cardiac Conduction Tissue in Pig and Man. GEORGE LUMB and HENRY SINGLETARY, Wilmington, North Carolina.

Distribution of Blood Flow in Canine and Human Hearts. LLOYD D. MACLEAN, YOUNG SONG KIM, and PAUL H. HEDENSTROM, St. Paul.

Basic Factors Related to the Experimental Production of Channels Collateral to the Coronary Arteries. WILLIAM H. SEWELL, Oteen, North Carolina.

A New Therapeutic Approach to Acute Coronary Occlusion. JOHN ARTHUR JACOBEY, WARREN J. TAYLOR, GEORGE THOMAS SMITH, RICHARD GORLIN, and DWIGHT E. HARKEN, Boston.

Lysis of Experimental Coronary Thrombi. JOHN L. KLINE and NILS M. OHLSSON, Philadelphia.

Distal Relocation of the Origin of the Left Coronary Artery by Subclavian-Coronary Artery Anastomosis. RICHARD T. MAMIYA, THEODORE COOPER, VALLEE L. WILLMAN, J. GERARD MUDD, and C. ROLLINS HANLON, St. Louis.

Effect of Pulmonary Artery-Left Atrium Shunts on Ischemic Hearts—Experimental Study and Clinical Application. AYDIN BILGUTAY, LUIS H. SANCHEZ, DAVID L. SIEGAL, and C. WALTON LILLEHEI, Minneapolis.

Immediate and Late Effects of Ligation of the Septal Artery on Perfusion of the Interventricular Septum. ARTHUR L. ROZMAN and JACKSON H. STUCKEY, Brooklyn.

Effect of Acute Aortic Insufficiency on the Myocardium. J. LEONEL VILLAVICENCIO and RICHARD WARREN, West Roxbury, Massachusetts.

Detection of Valvular Regurgitation by a Precordial Dilution Technique. ROLAND FOLSE, EUGENE BRAUNWALD, and MAURICE M. AYGEN, Bethesda.

Reflex Alterations in Cardiac Performance During Complete Heart Block. STANLEY K. BROCKMAN, Nashville.

Postpericardiotomy Syndrome; Observations Regarding Autoimmune Mechanisms in Its Etiology. ROBERT SCHRAMEL, WALTER WILLIAMSON, JR., FLAVIO IGLESIAS, and OSCAR CREECH, JR., New Orleans.

Wednesday, 8:30 a.m.—12:00 noon

TISSUE AND ORGAN TRANSPLANTATION

Effects of Function on Grafts of Autologous and Homologous Connective Tissue. WILLIAM W. KRIPPAEHNE, THOMAS K. HUNT, DAVID S. JACKSON, and J. ENGLEBERT DUNPHY, Portland, Oregon.

Effect of Ribonucleic Acid on Homograft Survival. WELDON B. JOLLEY, DAVID B. HINSHAW, and MERLE PETERSON, Los Angeles.

Immunologic Tolerance to Maternal Tissues Produced by Alterations in Placental Permeability. JOHN S. NAJARIAN and FRANK J. DIXON, Pittsburgh.

Acquired Tolerance by Repeated Parabiosis. CREIGHTON A. HARDIN and ALVAR A. WERDER, Kansas City, Kansas.

Homograft Tolerance in Adult Mice. RONALD D. GUTTMANN, San Francisco, GERALD J. VOSIKA, and J. BRADLEY AUST, Minneapolis.

Host Desensitization as a Means of Augmenting Tissue Homotransplantation. FOSTER MARSHALL, Columbus.

Antigenic Relationship Between Skin and Free Ovarian Homografts. DONALD P. GOLDSTEIN, DAVID C. MARSHALL, and SOMERS H. STURGIS, Boston.

An Epinephrine Test for Evaluating the Functional Survival of Splenic Transplants in Dogs. J. C. PIERCE, G. L. MACDONALD, and RICHARD L. VARCO, Minneapolis.

Biochemical Studies of the Homotransplanted Canine Liver. J. C. KUKRAL, M. H. LITTLEJOHN, G. W. BUTZ, JR., and T. E. STARZL, Chicago.

An Evaluation of Heterologous Tissue in Parathyroid Deficiency. STANLEY W. JACOB, ROBERT L. WEBB, MOHAMAD J. RASTEGAR, and J. ENGLEBERT DUNPHY, Portland, Oregon.

Effect of Cancer Chemotherapeutic Agents on the Survival of Homografts of Skin. WARREN R. SUTTON, HEROLD B. GRIFFITH, and FREDERICK W. PRESTON, Chicago.

Inhibition of the Rejection of Renal Homografts in Dogs by Burroughs Wellcome 57-322. ROY YORKE CALNE and JOSEPH E. MURRAY, Boston.

Homotransplantation of the Lung in Dogs Treated with Methotrexate. DAVID A. BLUMENSTOCK, JOHN A. COLLINS, E. DONNALL THOMAS, and JOSEPH W. FERREBEE, Cooperstown, New York.

Wednesday, 8:30 a.m.—12:00 noon

METABOLISM

Influence of Hypophysectomy on Energy Expenditure in Normal and Complicated Convalescence. RONALD G. CLARK, ALVARO RABELO, JOHN M. KINNEY, and HARVEY A. ZAREM, Boston.

Investigation of Aerobic Metabolism in Surgical Patients; Citrate Tolerance Studies. WILLIAM R. DRUCKER, BRYANT KINGSBURY, JAMES W. CRAIG, NANCY HOFMANN, and HIRAM WOODWARD, JR., Cleveland.

Immediate Influence of Propylthiouracil on Oxygen Consumption in the Dog. JESSE H. MEREDITH, HOBART ROGERS, and FRANK R. JOHNSTON, Winston-Salem.

Radioactive Oxygen-15 in the Tracer Study of Oxygen Transport. JOHN S. SPRATT, JR., MICHEL TER-POGOSSIAN, SANFORD RUDMAN, and ANDREW SPENCER, St. Louis.

Observations on Effects of Anesthesia on B Complex Vitamin Levels in Tissue. MAXIMO DEYSINE, HERMAN BAKER, OSCAR FRANK, CHARLES C. ABBOTT, EARL J. HALLIGAN, and CARROLL M. LEEVY, Jersey City.

Cellular Metabolism of Surviving Tissue Slices Following Various Types of Anesthesia. ROBERT ALEXANDER MACBETH, FRANK CECIL HALEY, and JULIUS GEORGE BEKESI, Edmonton.

Movement of Water Through Skin; Rate of Transfer in an Atmosphere of 100 Per Cent Saturation with Deuterium Oxide. WILLIAM A. NEELY, M. D. TURNER, J. D. SMITH, and JOHN WILLIAMS, Jackson.

Electronic Measurement of Total Free Ion Concentration of Body Fluids. JOSEPH C. DARIN and KENNETH KAYSER, Milwaukee.

Radioiodine-125 for Evaluation of Thyroid Function. PRENTISS M. DETTMAN and WILLIAM G. MYERS, Columbus, Ohio.

Activators and Inhibitors of Carbon 21 Steroid Hydroxylation by Adrenocortical Microsomes. D. Y. COOPER, O. FOROFF, and O. ROSENTHAL, Philadelphia.

Estimation of Aldosterone in Small Human Peripheral Venous Samples. WALTER H. MORAN, JR., A. MARTINSON, Morgantown, and BERNARD ZIMMERMANN, Minneapolis.

Metabolic Effect of an Anabolic Steroid, Norpropandrolate (SC-7525), in Experimental Acute Renal Failure. WATTS R. WEBB and VICENTE C. DEGUZMAN, Jackson.

Wednesday, 8:30 a.m.—12:00 noon

OLIGEMIC HYPOTENSION

Changes in the Hepatic Circulation with Graded Hemorrhage, Retransfusion, and Blood Volume Overexpansion; an Experimental Study in the Dog. WALTER MULLER and LOUIS L. SMITH, Los Angeles.

Measurement of Effective Circulating Volume and Total Circulating Volume in Normovolemic Hemorrhagic Shock. JOSEPH M. ST. VILLE and WILLIAM C. SHOEMAKER, Chicago.

Effect of *p*H Control on the Course of Hemorrhagic Shock. D. HASSAM, G. G. NAHAS, W. M. MANGER, and DAVID V. HABIF, New York.

Effect of Tris (Hydroxymethyl) Amino Methane (THAM) on the Renal Blood Flow During Hemorrhagic Shock. CARLOS A. SELMONOSKY, ROBERT H. GOETZ, and DAVID STATE, New York.

Effect of Guanethidine on Urinary Flow and Blood Pressure Following Arterial Hemorrhage in Dogs. JOHN H. WULSIN, DIETHARD W. GRUHL, and WILLIAM A. ALTEMEIER, Cincinnati.

Distribution of Blood in Prolonged Oligemic Hypotension. MICHAEL G. WEIDNER, JR., and FIORINDO A. SIMEONE, Cleveland.

Effect of Vasopressors on Renal Function in Acute Oligemia. K. T. HEMADY, ROBERT W. HOPKINS, and FIORINDO A. SIMEONE, Cleveland.

Effects of Arfonad on Regional Blood Flow. HAROLD L. FEIKES, C. ERWIN SYPHERS, and DAVID B. HINSHAW, Los Angeles.

Correction of the Oliguric Response to Trauma with Ten Per Cent Mannitol. NEIL LEMPERT, ANTONIO BOBA, and SAMUEL R. POWERS, JR., Albany.

Effects of Aldosterone in Therapy of Endotoxin Shock. CONRADO C. BONDOC, CHARLES C. WOLFERTH, JR., and GEORGE BESKID, Philadelphia.

Continuous Monitoring of Venous Pressure in Optimal Blood Volume Maintenance. JOHN N. WILSON and J. CUTHBERT OWENS, Albuquerque.

Wednesday, 1:30—5:00 p.m.

PHYSIOLOGY OF THE LIVER; PORTAL HYPERTENSION

Relationship and Significance of the Levels of Direct Bilirubin, Indirect Bilirubin, and Alkaline Phosphatase in Lymph, Blood, and Urine After Ligation of the Common Bile Duct. FIKRI ALICAN and JAMES D. HARDY, Jackson.

Effect on the Gallbladder and the Liver of Temporary Occlusion of the Common Bile Duct in Dogs. JOHN V. PIKULA and MAURICE J. ELOVITZ, Boston.

Source of Hyperalkaline Phosphatasemia Following Experimental Occlusion of the Hepatic Duct. STANTON G. POLIN, S. LLOYD TEITELMAN, MITCHELL A. SPELLBERG, and MAKOTA OKUMURA, Chicago.

Function Studies of Liver Autotransplants. BERNARD SIGEL, LORENZO J. BREA, and MARVIN R. DUNN, Philadelphia.

Studies of Liver Cell Function in Cirrhosis. JEROME H. SACKS and DAVID M. HUME, Richmond.

Hepatic Potassium Release. HARRY H. LEVEEN and GERALD FALK, Brooklyn.

Metabolic Observations During Continuous Intravenous Infusion of Ascitic Fluid. HAROLD KING, ROBERT E. LEMPKE, ROBERT D. KING, and GEORGE C. KAISER, Indianapolis.

Further Observations on Thoracic Transposition of the Spleen. JOHN H. FOSTER, WILLIAM S. STONEY, and H. WILLIAM SCOTT, JR., Nashville.

Hepatolienopexy—a Method of Portal Decompression. F. BEACHLEY MAIN and JOHN H. FOSTER, Nashville.

Pressure-Flow Studies in the Isolated, Perfused Calf Liver. ROBERT E. CONDON, NILES D. CHAPMAN, LLOYD M. NYHUS, and HENRY N. HARKINS, Seattle.

Studies on the Reactivity of the Portal Venous System in Experimental Portal Hypertension. GERALD W. PESKIN, LEONARD D. MILLER, LEROY L. JOHNSON, HORACE MACVAUGH III, and W. H. HARDESTY, Philadelphia.

Hemodynamic Data on Patients Undergoing Portacaval Anastomosis for Ascites. MARVIN L. GLIEDMAN, ROBERT D. SELLERS, JOSEPH S. BURKLE, and IRVING F. ENQUIST, Brooklyn.

Wednesday, 1:30—5:00 p.m.

FACTORS INFLUENCING PULMONARY CIRCULATION AND VENTILATION

Pulmonary Membrane Injury During Surgery. LOIS T. ELLISON, ALTON R. NIX, and ROBERT G. ELLISON, Augusta, Georgia.

Pulmonary Damage Resulting from Pulmonary Arterial Ischemia. DAVID M. LONG, JR., RICHARD L. CLANCY, and E. B. BROWN, JR., Minneapolis.

Pulmonary Changes Secondary to Prolonged Perfusion. A. KONTAXIS, R. TOMIN, B. WITTLES, WILLIAM E. NEVILLE, and GEORGE H. A. CLOWES, JR., Cleveland.

Effects of Atelectasis upon Pulmonary Blood Flow. HORACE MACVAUGH III, W. H. HARDESTY, W. E. DEMUTH, E. YALAV, and WILLIAM S. BLAKEMORE, Philadelphia.

Alterations in Cardiopulmonary Physiology Following Autotransplantation of the Lung. SALVATORE L. NIGRO, ARTHUR F. REIMANN, WILLARD A. FRY, L. FARRELL MOCK, and WILLIAM E. ADAMS, Chicago.

Blood Flows in Dependent Versus Nondependent Lungs in Human Beings With and Without Mitral Valve Disease. HOWARD B. KEITH, GUNNAR SEVELIUS, PHILLIP C. JOHNSON, and GILBERT S. CAMPBELL, Oklahoma City.

Use of Free Atrial Graft for Outflow Tract Roof of the Right Ventricle. DONALD G. MULDER, JOHN C. MIETHKE, and THOMAS CHARBONNEAU, Los Angeles.

Valvular Prosthesis for Prevention of Pulmonary Regurgitation in Correction of the Pulmonary Stenosis in Tetralogy of Fallot. LUIS H. SANCHEZ, AYDIN M. BILGUTAY, DAVID L. SIEGAL, and C. WALTON LILLEHEI, Minneapolis.

Influence of Maturity of the Pulmonary Vessels on the Response to a Systemic to Pulmonary Artery Anastomosis. JOHN W. RICHARDSON, CLAY E. PHILLIPS, JR., JAMES A. DEWEESE, JAMES A. MANNING, and EARLE B. MAHONEY, Rochester, New York.

Experimental Production of Pulmonary Artery Atherosclerosis. SAM E. STEPHENSON, JR., and RACHEL YOUNGER, Nashville.

Effects of Synthetic Angiotensin on the Cardiovascular System in Dogs. JOHN R. DERRICK, JAMES R. ANDERSON, Galveston, and GUNTER CORSSEN, Ann Arbor.

Significance of Tracheal Collapse in Pulmonary Emphysema—Cinefluorographic Observations. W. GERALD RAINER, ROGER S. MITCHELL, GILES F. FILLEY, Denver, and BEN EISEMAN, Lexington.

Wednesday, 1:30—5:00 p.m.

OBSTETRICS AND GYNECOLOGY

Placental Transfer of Pituitary and Adrenal Hormones. BENJAMIN T. JACKSON and RICHARD H. EGDAHL, Richmond.

Modification of Maternal Host-Adult Homograft Interactions by Massage of Uteroplacental Sites Prior to Grafting. RICHARD H. ANDRESEN, GEORGE M. HASS, DOROTHY A. MADDEN, and SOPHIA SWARTZBAUGH, Chicago.

Correlation of Column Chromatographic and Alkali Denaturation Methods for the Determination of Fetal Hemoglobin in Cord Blood. DAVID H. ARMSTRONG and W. A. SCHROEDER, Pasadena.

Acid Base Equilibrium of Mother and Fetus in Utero During Diffusion Respiration. WARREN E. COOPER, Denver.

Effect of Hypoxia on Fetal Electrocardiogram and Tissue Oxygen Tension. TSUYOSHI KANEOKA, SEYMOUR L. ROMNEY, and PAUL V. GABEL, New York.

Serum Sodium and Total Solute Concentrations in Normal and Toxic Pregnancy. WAYNE L. JOHNSON, HARRY S. MCGAUGHEY, JR., and WILLIAM N. THORNTON, JR., Charlottesville.

Observations on the Use of 17-Alpha-Hydroxy-Progesterone Caproate on Primary and Metastatic Endometrial Carcinoma. ROBERT W. KISTNER and SUZANNE BAGINSKY, Brookline.

The Function of Ovarian Homografts in Cornea Chambers. HECTOR CASTELLANOS and SOMERS H. STURGIS, Boston.

Positive Assessment of Tumor Response in Patients with Abdominal Visceral Metastases. EDWARD L. SELJESKOG, DEMETRE M. NICOLOFF, and CLAUDE R. HITCHCOCK, Minneapolis.

Technical Considerations in the Treatment of Pelvic Cancer by Continuous Intra-arterial Infusion. GEORGE S. RICHARDSON and HOWARD ULFELDER, Boston.

A New Procedure for Recurrent Carcinoma of the Cervix. CONDICT MOORE, Louisville.

Experiences with a Pelvic Tourniquet in Man. DANIEL S. MARTIN, JAMES C. HOBBS II, HAYES MACMURRY WHITE, JR., and JAMES PICKENS, Miami.

UNIVERSITY OF MICHIGAN LIBRARIES

Thursday, 8:30 a.m.—12:00 noon

UROLOGY

Adrenal Function in Patients with Lesions High in the Spinal Cord. William Osborn, Harry W. Schoenberg, John J. Murphy, William J. Erdman III, and David Young, Philadelphia.

Some Observations on Renal Blood Flow and Its Dependence on Fluid Administration. Victor R. Goeller and Jorgen U. Schlegel, New Orleans.

Reversal of Hypertension from Segmental Renal Ischemia by Ligation of the Segmental Artery. Paulo P. deMendonca and John D. Young, Jr., Baltimore.

A New Individual Renal Clearance Test Using Radioiodohippurate. Chester C. Winter, Columbus, Ohio.

Approximation and Dilatation; the Mode of Healing of an Unintubated Ureterotomy. Stephen A. Mahoney and Lester Persky, Cleveland.

Deuterium Oxide Absorption Studies in Man and Experimental Animals. William C. Garre and William A. Neely, Jackson.

In Vitro Study of the Wisconsin Bovine Bladder Tumor. Robert U. Bregman and Eleanor T. Bregman, Los Angeles.

Immunologic Studies on Naphthalamine Carcinogens. Robert Ollodart and Noel R. Rose, Buffalo.

Pelvic Perfusion—II, the Acute Effect of Isolated Perfusion with Diphenylthiocarbozone (Dithizone) on the Canine Prostate. Milton B. Myers, George R. Prout, Jr., Richmond, and Daniel S. Martin, Miami.

Heterotopic Ossification in Uroepithelial Regeneration on Grafts of Ileum and Colon. John P. Blandy and James H. McDonald, Chicago.

Quantitation of Urethral Resistance. James M. Pierce, Jr., and Esmond Braun, Detroit.

Experimental Torsion of the Spermatic Cord. Lewis P. Sonda, Jr., and Jack Lapides, Eloise, Michigan.

Thursday, 8:30 a.m.—12:00 noon

PEPTIC ULCER; TECHNIQUES OF GASTROINTESTINAL STUDY

Esophageal Hiatus Hernia and Esophagitis; an Evalution of Treatment by Inhibiting Reflux of Acid-Peptic Gastric Contents. Fletcher A. Miller and Manuel Veloso, Minneapolis.

Effect of Carrageenin on Mann-Williamson Ulcer in Dogs. Julius A. Mackie, Jr., Horace MacVaugh III, and L. T. Patterson, Philadelphia.

Completeness of Vagotomy as Judged by Postoperative Studies of Gastric Pepsin Concentration. Thomas F. Silva, Jr., Douglas A. Farmer, and Reginald H. Smithwick, Boston.

Iron Absorption from Food After Subtotal Gastrectomy in the Dog. Earl E. Cammock, Adam Turnbull, Cloyde L. Fausnaugh, Frans J. Cleton, Lloyd M. Nyhus, Clement A. Finch, and Henry N. Harkins, Seattle.

The Duodenum and the Intestinal Phase of Gastric Secretion. Ward O. Griffen, Jr., Demetre M. Nicoloff, Nelson H. Stone, Aldo Castaneda, and Owen H. Wangensteen, Minneapolis.

Techniques for Making Autografts of the Stomach, with Notes on Their Function. Richard C. Lillehei, Jerrold K. Longerbeam, and Bernard Goott, Minneapolis.

A Method of Reproducing the Pavlov Pouch Technique in Man. Daniel Shapira, Jordan Haller, and David State, New York.

An Experimental Method of Precisely Defining the Dimensions of the Gastric Antrum. Edward M. Lowicki and James B. Littlefield, Charlottesville.

Experimental Studies of the Effects of Saliva on Components of the Gastric Secretions. Stanley C. Skoryna, E. D. McSweeney, D. M. Edward, and Donald R. Webster, Montreal.

The Silicone-Foam Diagnostic Enema. Galen B. Cook and Alexander R. Margulis, St. Louis.

Thursday, 8:30 a.m.—12:00 noon

VASCULAR SURGERY

Experimental Observations on Total Prosthetic Reconstruction of the Aortic Valve. Richard E. Larson and Dwight C. McGoon, Rochester, Minnesota.

Influence of Aortic Insufficiency on Experimental Atherosclerosis. Joseph L. Kovarik, J. Philip Clarke, and Robert L. Hawley, Denver.

Experimental Atherosclerosis Produced by Alteration of Blood Vessel Configuration. Anthony M. Imparato, Jere W. Lord, Jr., Meyer Texon, and Milton Helpern, New York.

Susceptibility of Autologous Vein Grafts to Atheromatous Degeneration. Yoshio Sako, Minneapolis.

Effect of Fibrinolytic Agents on the Thrombosis Rate of Prosthetic Grafts in Small Arteries; an Experimental Study. ROBERT B. ATWELL, ELDEN L. MOHR, DAVID JACOBS, and BERNARD FISHER, Pittsburgh.

Relative Ability of Different Conductive Surfaces to Repel Clot Formation on Intravascular Prostheses. JOHN R. SADD, DONALD E. KOEPKE, RONALD L. DAGGETT, WILLIAM C. ZARNSTORFF, WILLIAM P. YOUNG, and VINCENT L. GOTT, Madison.

Control of Vascular Anastomotic Hemorrhage in Heparinized Dogs with a Rapidly Polymerizing Adhesive. H. EDWARD GARRETT and SAM W. LAW, Houston.

Results of Small Artery Endarterectomy—Microsurgical Technique. ERNESTO L. SUAREZ and JULIUS H. JACOBSEN II, Burlington, Vermont.

Use of an Autogenous Vein Patch in the Performance of End-to-End Anastomoses in Small Arteries. AUGUSTO R. DE LEON, PAUL S. CRANE, and FRANK C. SPENCER, Baltimore.

Peripheral Vein Grafts in Dogs. DONALD SILVER and WILLIAM G. ANLYAN, Durham.

Experimental Thrombosis of the Canine Femoral Artery—I, Hemodynamic Studies. ELIAS A. HUSNI, Washington.

Role of the Renal Arterial Pulse Pressure in Renal Hypertension. JOHN R. CAMPBELL and PAUL R. SCHLOERB, Kansas City, Kansas.

Mechanism of Hypotension Following Release of Abdominal Aortic Clamps. LLOYD E. RADER, JR., HOWARD B. KEITH, and GILBERT S. CAMPBELL, Oklahoma City.

Thursday, 8:30 a.m.—12:00 noon

NEUROLOGIC SURGERY

Hypothalamic Lesions and Acute Gastric Ulceration. DONLIN M. LONG, ARNOLD S. LEONARD, DEMETRE M. NICOLOFF, LYLE A. FRENCH, and OWEN H. WANGENSTEEN, Minneapolis.

Experimental Hyperphagia Following Destructive Midbrain Lesions in Cats. F. MILES SKULTETY and THOMAS GARY, Iowa City.

A New Ascending Spinal Trigeminal Neural Pathway. WILLIAM A. STEWART and ROBERT B. KING, Syracuse.

Electroanalgesia (Electronarcosis) in the Experimental Animal. GEORGE W. SMITH, ROBERT SMITH, PERRY VOLPITTO, CRAIG GOODWIN, and ZACK GRAMLING, Augusta, Georgia.

Effect of Sympathetic Stimulation on Cerebral Oxygen Tension. BYRON M. BLOOR, FRANK HELLINGER, and GEORGE C. STEVENSON, Morgantown.

Treatment of Experimental Carotid Emboli by Regional Extracorporeal Perfusion with Fibrinolysin. M. S. MAHALEY, JR., WIILLIAM T. WEAVER, BARNES WOODHALL, and WILLIAM G. ANLYAN, Durham.

Histochemical and Quantitative Analysis of Alkaline Phosphatase During the Course of Experimental Intracranial Neoplasia. WOLFF M. KIRSCH, St. Louis.

Results of Intermittent, Prolonged Infusion of Nitrogen Mustard into the Carotid Artery in Twelve Patients with Cerebral Gliomas. IMRAN HATIBOGLU and GUY OWENS, Buffalo.

Mechanism of Action of Urea; Accumulation of Urea in the Brain and Shift in Electrolytes and Water. BYRON W. ROVINE and WILLIAMINA A. HIMWICH, Galesburg.

Use of Hypertonic Mannitol Solutions to Lower Cerebrospinal Fluid Pressure and Decrease Brain Bulk in Man. BURTON L. WISE and NORMAN CHATER, San Francisco.

Fractional Pneumoencephalography—a Comparative Study. NICHOLAS WETZEL, SANFORD LARSON, and RUBEN BROCHNER, Chicago.

Carotid Arteriography by Percutaneous, Retrograde Injection of the Contrast Medium. JOHN S. COLLIS, JR., and W. JAMES GARDNER, Cleveland.

Thursday, 1:30—3:00 p.m.

NEUROLOGIC SURGERY

Electrical and Behavioral Changes Following Thalamotomy. MARION F. JURKO and ORLANDO J. ANDY, Jackson.

Aneurysm of the Anterior Communicating Artery—Results of Surgical Treatment. EDWIN F. LANG, JR., and JAMES L. POPPEN, Boston.

Use of Fluoresceine for the Diagnosis and Localization of Cerebrospinal Fluid Fistulas. F. R. KIRCHNER, Kansas City, Kansas.

Tolerance of Anoxia of the Dog's Brain at Various Temperatures. ROBERT J. BOYD and JOHN E. CÓNNOLLY, Palo Alto.

Vascular Resistance and Oxygen Utilization of the Brain, Heart, and Whole Body in Profound Hypothermia. EDGAR A. BERING, JR., WILLIAM F. BERNHARD, HANS F. SCHWARZ, and CARL H. SUTTON, Boston.

Survival of Hamsters After Four Hours of Cardiac Arrest at 0 Degrees C. CHARLES E. HUGGINS, Boston.

UNIVERSITY OF MICHIGAN LIBRARIES

Television Program

Color telecasts, dating back only to 1949, have also come a long way. Now the unique, three-way discussion between operating surgeon, moderator and panel, and audience, has made this portion of the program popular and useful.

Monday, 10:00—11:30 a.m.

Cardiac Procedure. PETER V. MOULDER, Chicago.
Moderator: DENTON A. COOLEY, Houston.
Panelists: JOHN E. CONNOLLY, San Francisco, JAMES A. HELMSWORTH, Cincinnati, and JACK A. CANNON, Los Angeles.

Monday, 2:00—3:30 p.m.

Radical Mastectomy with Internal Mammary Dissection. DONALD J. FERGUSON, Chicago.
Moderator: RUDOLF J. NOER, Louisville.
Panelists: JEROME A. URBAN, New York, O. THERON CLAGETT, Rochester, Minnesota, and WALTER J. BURDETTE, Salt Lake City.

Monday, 3:30—5:00 p.m.

Stereotaxic Procedure. JOHN F. MULLAN, Chicago.
Moderator: IRVING S. COOPER, New York.
Panelists: RUSSELL MEYERS, Iowa City, GEORGE M. AUSTIN, Portland, Oregon, and NICHOLAS WETZEL, Chicago.

Tuesday, 10:00—11:30 a.m.

Operation for Disease of the Esophagus. WILLIAM A. ADAMS, Chicago.
Moderator: FREDERICK D. KERGIN, Toronto.
Panelists: IVAN D. BARONOFSKY, San Diego, ROBERT P. MCBURNEY, Memphis, and HERBERT D. ADAMS, Boston.

Tuesday, 2:00—3:30 p.m.

Operation for Peptic Ulcer. WYNN SAYMAN, Chicago.
Moderator: JOHN H. MULHOLLAND, New York.
Panelists: CLARENCE J. BERNE, Los Angeles, J. LYNWOOD HERRINGTON, JR., Nashville, and JACK M. FARRIS, Los Angeles.

Tuesday, 3:30—5:00 p.m.

Total Adrenalectomy for Advanced Malignancy of the Breast. PAUL V. HARPER, Chicago.
Moderator: VICTOR RICHARDS, San Francisco.
Panelists: HAROLD G. BARKER, New York, NORMAN TREVES, New York, and ROGER D. WILLIAMS, Columbus, Ohio.

Wednesday, 10:00—11:30 a.m.

Pulmonary Resection. ROBERT W. HARRISON, Chicago.
Moderator: WILSON WEISEL, Milwaukee.
Panelists: JOHN F. HIGGINSON, Santa Barbara, DONALD L. PAULSON, Dallas, and WILLIAM L. WATSON, New York.

Wednesday, 2:00—3:30 p.m.

Intestinal Resection. JOHN VAN PROHASKA, Chicago.
Moderator: STANLEY R. FRIESEN, Kansas City, Kansas.
Panelists: ALLEN M. BOYDEN, Portland, Oregon, JOHN RAKER, Boston, and JOHN A. SCHILLING, Oklahoma City.

Wednesday, 3:30—5:00 p.m.

Operation for Kidney Disease. EDWARD S. LYON, Chicago.
Moderator: WILLIAM C. BAUM, Grand Rapids.
Panelists: EDUARDO CASTRO, Mexico City, RUBIN H. FLOCKS, Iowa City, and B. G. CLARKE, Boston.

Thursday, 10:00—11:30 a.m.

Cesarean Section. M. EDWARD DAVIS, Chicago.
Moderator: RALPH E. CAMPBELL, Madison.
Panelists: EDWARD A. BANNER, Rochester, Minnesota, GEORGE F. MELODY, San Francisco, and STUART ABEL, Chicago.

Thursday, 2:00—3:30 p.m.

Laryngectomy. WILLIAM G. HEMENWAY, Chicago.
Moderator: EDGAR L. FRAZELL, New York.
Panelists: CALVIN T. KLOPP, Washington, JOSEPH H. OGURA, St. Louis, and JOHN J. CONLEY, New York.

Friday, 10:00—11:30 a.m.

Regional Perfusion for Carcinoma. GEORGE E. BLOCK, Chicago.
Moderator: WILLIAM W. SHINGLETON, Durham.
Panelists: CLAUDE R. HITCHCOCK, Minneapolis, JOHN HURLEY, Milwaukee, and EDWARD T. KREMENTZ, New Orleans.

Friday, 2:00—3:30 p.m.

Open Reduction for Fracture. ROBERT D. MOORE, Chicago.
Moderator: PHILIP D. WILSON, New York.
Panelists: OTTO E. AUFRANC, Boston, DONALD L. EYLER, Nashville, and THOMAS B. QUIGLEY, Boston.

Friday, 3:30—5:00 p.m.

Construction of Ileal Pouch for Urinary Diversion. JOHN L. SOMMER, Chicago.
Moderator: WILLARD E. GOODWIN, Los Angeles.
Panelists: ALEXANDER H. BILL, JR., Seattle, WYLAND F. LEADBETTER, Boston, and KENNETH M. LYNCH, Charleston.

Motion Picture Exhibition

Selected films, approved by the College's Committee on Motion Pictures, will be shown throughout the week. The advance schedule follows.

Monday, 8:30 a.m.—12:30 p.m.

NICHOLAS WETZEL, Chicago, *Presiding*.
By Special Request: Resuscitation of the Newborn. Sponsored by the Committee on Infant Mortality, New York Medical Society.
Cardiac Monitoring. DENTON A. COOLEY, Houston.
Induced Fibrillatory Heart Arrest. WILLIAM L. GLENN, New Haven.
By Special Request: External Cardiac Massage.
Complications of Atherosclerosis. JAMES D. HARDY, Jackson.
Pericardectomy. JOHN L. MADDEN, New York.
Ureteral Implantation. WYLAND F. LEADBETTER, Boston.
Median Nerve Decompression. JOHN L. SCHNEEWIND, Chicago.
Thumb Reconstruction by Toe Transfer. BROMLEY S. FREEMAN, Houston.
Spondylolisthesis. BEN R. WILTBERGER, Columbus.

Monday, 1:30—5:00 p.m.

T. HOWARD CLARKE, Chicago, *Presiding*.
Stamp Out Operating Room Staphylococcus. RALPH ADAMS, Wolfeboro, N. H.
Myasthenia Gravis. JOHN L. MADDEN, New York.
Surgical Regional Chemotherapy. ROBERT K. AUSMAN, Buffalo, and BRADLEY AUST, Minneapolis.
Ulcerogenic Tumor of the Pancreas. ROBERT M. ZOLLINGER, Columbus.
Pseudocyst of the Pancreas. FREDERICK E. KREDEL, Charleston.
Postinflammatory Pancreatic Pseudocyst: Treatment by Transvisceral Cystoenterostomy. MELVIN P. OSBORNE, Brookline.

Tuesday, 1:30—5:00 p.m.

EDWARD STARR JUDD, Rochester, Minnesota, *Presiding*.
Surgical Treatment of Abdominal Angina. WATTS R. WEBB, Jackson.
Preperitoneal Hernioplasty. LLOYD M. NYHUS, Seattle.
Technique of Repair of Direct Inguinal Hernia. JOHN L. MADDEN, New York.
Diagnostic Proctostomy. CHARLES H. BROWN, Cleveland.
Billroth I—Gastric Resection. STANLEY HOERR, Cleveland.
Total Gastrectomy with Jejunal Interposition. JOHN M. BEAL, New York.

UNIVERSITY OF MICHIGAN LIBRARIES

Transcolonic Resection for Esophageal Atresia. FRITZ LINDER, Berlin.
Ventricular Septal Defects. DENTON A. COOLEY, Houston.

Wednesday, 1:30—5:00 p.m.

RUDOLF J. NOER, Louisville, *Presiding.*
Stapedectomy. HAROLD F. SCHUKNECHT, Detroit.
Combined Abdominal Perineal Resection. FRANCIS D. MOORE, Boston.
Colostomy. RUPERT TURNBULL, Cleveland.
Polyps of the Large Intestine. R. J. JACKMAN, Rochester, Minnesota.
Surgery of Cancer of the Colon. RUPERT TURNBULL, Cleveland.
One Stage Repair of Hypospadias. CHARLES J. DEVINE, JR., Norfolk.

Thursday, 1:30—5:00 p.m.

Pediatric Films.
ORVAR SWENSON, Chicago, *Presiding.*
Pyloric Stenosis. HUGH B. LYNN, Rochester, Minnesota.
Rupture of Stomach in Newborn. WILLIAM J. GROVE, Chicago.
Trichobezoar. HUGH B. LYNN, Rochester, Minnesota.
Aneurysm of Jugular Vein. ROWENA SPENCER, New Orleans.
Diaphragmatic Hernia in the Newborn. J. L. EHRENHAFT, Iowa City.
Anomalies of Umbilicus. ROWENA SPENCER, New Orleans.
Omphalocele. HUGH B. LYNN, Rochester, Minnesota.
Atresia of the Intestine. DONALD GLOVER, Cleveland.
Megacolon. HUGH B. LYNN, Rochester, Minnesota.
Perineal Anomalies. DONALD GLOVER, Cleveland.

Friday, 8:30 a.m.—12:30 p.m.

WILLIAM G. PACE, Columbus, *Presiding.*
The Peritoneum; Reactions to Operative Trauma and Their Control. JOHN A. GIUS, Iowa City.
Procedure of Choice in Duodenal Ulcer Problems. R. CAMERON HARRISON, Edmonton.
Strangulated Obstruction of the Intestine. HAROLD LAUFMAN, Chicago.
Large Bowel Obstruction. FRAZER N. GURD, Montreal.
Fluid Balance in Gastrointestinal Surgery. ROBERT M. ZOLLINGER, Columbus.
Ureteral Injuries. CHARLES C. HIGGINS, Cleveland.
Acute Head Injury. JOSEPH P. EVANS, Chicago.

Scientific Exhibition

Pick-Congress Hotel

Computers and Medical Record Data. VERGIL N. SLEE, Commission on Professional and Hospital Activities, Ann Arbor.
American Hospital Association, Chicago.
Unproved Cancer Therapy. ROALD N. GRANT, JOHN F. W. KING, and I. L. BARTLETT, American Cancer Society, New York.
Localization of the Cardiac Conduction System. WILLIAM F. BERNHARD, ALBERT M. GRASS, and S. EDWIN CARROLL, Children's Hospital Medical Center, Boston.
Cardiac Arrest—Management. DENIS CAVANAGH, ROBERT S. LITWAK, and JAMES H. FERGUSON, University of Miami School of Medicine, Miami.
Microvascular Surgery. SIL H. LEE and BERNARD FISHER, University of Pittsburgh, Pittsburgh.
Pathology of Congenital Heart Disease. MAURICE LEV, BESSIE L. LENDRUM, and BENJAMIN M. GASUL, Hektoen Institute for Medical Research and Cook County Children's Hospital, Chicago.
Portal Hypertension in Children. RICHARD PANG, F. J. HARBERG, and LUKE W. ABLE, Baylor University College of Medicine, Houston.
Mercury Strain Gauge Plethysmography. JOHN W. BELL, D. E. STRANDNESS, GERALD E. GIBBONS, and CHARLES J. EAGAN, Veterans Administration Hospital and University of Washington, Seattle.
Phlebography of Lower Extremities. O. C. KING and F. DANA LAW, Pennsylvania Hospital, Philadelphia.

Isotopic Evaluation of Portal Circulation. SEYMOUR I. SCHWARTZ, ROBERT H. GREENLAW, and RICHARD D. HOWE, University of Rochester School of Medicine and Dentistry, Rochester, New York.

Arterial Insufficiency in Vital Organs. ALLAN D. CALLOW, R. A. DETERLING, JR., and ROBERT PAUL, Tufts University School of Medicine and New England Center Hospital, Boston.

Management of Chest Injuries. ROBERT G. TROUT and JULIO C. DAVILA, Presbyterian Hospital and Fitzgerald Mercy Hospital, Philadelphia.

Unusual Common Duct Problems. CURTIS P. ARTZ, JAMES D. HARDY, and WILLIAM A. NEELY, University of Mississippi Medical Center, Jackson.

(1) Intestinal Decompression. (2) Gastric Blood Flow. OWEN H. WANGENSTEEN, DEMETRE M. NICOLOFF, EDWARD T. PETER, and ARNOLD S. LEONARD, University of Minnesota Hospitals, Minneapolis.

Bleeding Peptic Ulcer in Patients with Heart Disease. WILLIAM J. GRACE and WILLIAM F. MITTY, JR., St. Vincent's Hospital, New York.

Superior Mesenteric Artery Occlusion. B. B. JACKSON, University of Louisville School of Medicine, Louisville.

Surgical Complications of Atherosclerosis. WATTS R. WEBB, JAMES D. HARDY, and RUSSEL H. CANNON, University of Mississippi Medical Center, Jackson.

Peripheral Arteriosclerosis. A. W. HUMPHRIES, V. G. DE WOLFE, and F. A. LE FEVRE, Cleveland Clinic Foundation, Cleveland.

Chronic Atelectasis—Bronchoplastic Reinflation. JOHN R. BENFIELD, EDWIN T. LONG, and WILLIAM E. ADAMS, University of Chicago School of Medicine, Chicago.

Pectus Excavatum. N. K. JENSEN, W. ROBERT SCHMIDT, and J. J. GARAMELLA, University of Minnesota School of Medicine, Minneapolis.

Visual Estimation of Blood Loss During Surgery. WARNER H. GUSTAVSON and NELSON B. RUE, U.S.A.F. Aerospace Medical Center, Lackland Air Force Base, Florida.

Indications for Choledochostomy. GEORGE M. SAYPOL, New York University Medical Center, New York.

Control of Bleeding Peptic Ulcer. ROBERT T. MURPHY, JOSEPH L. BILTON, and EDWARD A. MARSHALL, Huron Road Hospital, Cleveland.

Diagnostic Approach to Upper Gastrointestinal Hemorrhage. WILLIAM W. NICHOL, EDDY PALMER, CANNON A. OWEN, and THEODORE R. SADLER, Brooke General Hospital, Fort Sam Houston.

Total Coloscopy. JOHN E. COGAN, JAMES HAMPTON, and J. WADE HARRIS, Hermann Hospital, Houston.

Advances in Surgical Treatment of Hearing Loss. CLAUDE L. PENNINGTON, Macon.

Preperitoneal Hernioplasty. LLOYD M. NYHUS, ROBERT E. CONDON, and HENRY N. HARKINS, University of Washington, Seattle.

Diaphragmatic Hernias. JAMES D. HARDY, WILLIAM C. GARRE, and JAMES M. GOODMAN, University of Mississippi Medical Center, Jackson.

Local Anesthesia in Colorectal Surgery. GUY L. KRATZER and JACK A. YOUNG, Allentown Hospital, Allentown.

Esophageal Reconstruction with Retrosternal Colon. CHARLES D. SHERMAN, JR., EARLE B. MAHONEY, and THEODORE I. JONES, University of Rochester School of Medicine and Dentistry, Rochester, New York.

Bleeding Esophageal Varices. STEPHEN L. WANGENSTEEN, RICHARD BERGLAND, and RICHARD ORAHOOD, Columbia University College of Physicians and Surgeons, New York.

Model Emergency Department. Committee on Trauma, American College of Surgeons (supported by Hartford Foundation), Chicago.

Blood Volume and Liver Function Measurement. B. BALKISSOON, E. HERR, and M. W. SPELLMAN, Howard University College of Medicine, Washington.

Autogenous Bone Cranioplasty. DARRELL T. SHAW and D. G. RICHEY, St. Luke's Hospital, Cleveland.

Ligation of Hypogastric Arteries in Pelvic Hemorrhage. WALTER J. REICH and MITCHELL J. NECHTOW, Cook County Hospital, Chicago.

Reconstructive Surgery of the Mandible. HERBERT CONWAY and DICRAN GOULIAN, JR., Cornell Medical Center, New York.

Salvage of the Rheumatoid Hand. ADRIAN E. FLATT, University of Iowa, Iowa City.

New Operation for Cleft Lip. SIDNEY K. WYNN, Milwaukee Children's Hospital, Milwaukee.

Thermal Burns of the Ears and Eyelids. PHILIP H. TAYLOR, LOUIS Q. PUGSLEY, and JOHN A. MONCRIEF, Brooke Army Medical Center, Fort Sam Houston.

Diagnostic Problems of Joints. Committee on Pathology, American Academy of Orthopedic Surgeons, M. BONFIGLIO, Chairman, Iowa City.

Medicine and Surgery in the Civil War. Library, American College of Surgeons, KATHLEEN WORST, Chicago.

Joint Commission on Accreditation of Hospitals. KENNETH B. BABCOCK and DENVER M. VICKERS, Chicago.

Reconstructive Urologic Surgery. WYLAND F. LEADBETTER and KHALIL TORBEY, Massachusetts General Hospital, Boston.

UNIVERSITY OF MICHIGAN LIBRARIES

"Choke" Voiding Excretory Cystourethrography. ROBERT O. PEARMAN and JERRY MILLER, University of California and Veterans Administration Hospital, Los Angeles.

Enzymatic Debridement in Burns. MILVIN SPIRA, ALBERTO SANCHEZ, and S. BARON HARDY, Baylor University College of Medicine, Houston.

Skin Grafts in Finger Tip Amputations. WILLIAM T. RUMAGE, JR., University of Louisville School of Medicine, Louisville.

Exposure Method of Skin Grafting. HERBERT D. GULLICK, Veterans Administration Hospital, Syracuse.

Plastic Surgery of the Nose. ANTHONY P. JEROME and JAMES W. WALKER, University of Tennessee Medical School, Memphis.

Central Fracture Dislocation of the Hip. FREDERICK G. HAMILTON, Huron Road Hospital, Cleveland.

Transabdominal Adrenalectomy. A. D. MCKENZIE and R. M. CHRISTENSEN, University of British Columbia, Vancouver.

Oncology of Head and Neck. RICHARD T. FARRIOR and GARLAND D. DUMMIT, Tampa.

En Bloc Bilateral Neck Dissection with Laryngectomy. DONALD A. CORGILL and BERNARD L. YOLLICK, Veterans Administration Hospital and University of Texas Southwestern Medical School, Dallas.

Cancer Chemotherapy. JOHN D. HURLEY and EDWIN H. ELLISON, Marquette University School of Medicine, Milwaukee.

Anoxia of the Femoral Head. CHARLES F. WOODHOUSE, Northwestern University, Chicago.

Parotid Tumors, Benign and Malignant. HARRY KOLSON, PHILIP COOPER, and JOHN LUCAS, Bronx Veterans Administration Hospital, New York.

Visualization of Placenta. RICHARD L. BERNSTINE, ROBERT B. SMALL, and CHARLES H. MOSELEY, JR., U.S. Naval Hospital, Portsmouth, Virginia.

Cancer Arising in Chronic Scars and Sinuses. J. M. YOUNG, R. F. BOWERS, and D. F. DAWSON, Veterans Administration Hospital, Memphis.

Chemotherapy of Metastatic Testis Cancer. WILLET F. WHITMORE, JR., MIN-CHIU LI, ROBERT GOLBEY, and A. R. MACKENZIE, Memorial Center for Cancer and Allied Diseases, New York.

Lymphography. MANUEL VIAMONTE, JR., RAYMOND E. PARKS, and MANUEL SOTO, University of Miami, Miami.

Experimental and Clinical Studies of Lymphatics. ROBERT BOWER, CALLISTO DANESE, and JOHN HOWARD, Hahnemann Medical College, Philadelphia.

Preservation and Transplantation of Bone Marrow. VICTOR RICHARDS and MAXIM PERSIDSKY, Presbyterian Medical Center, San Francisco.

Clinical and Experimental Use of Fibrinolysin. W. H. MEYER, JR., P. U. GERBER, and P. W. BOYLES, University of Miami Medical School, Miami.

The Diagnostic Peritoneal Tap. WILLIAM H. MORETZ, THOMAS C. MANN, and HAROLD S. ENGLER, Medical College of Georgia, Augusta.

Correlative Cholangiographic Anatomy. FRANK GLENN, FRANK G. MOODY, and THANE ASCH, The New York Hospital-Cornell Medical Center, New York.

Edema of Arm After Radical Mastectomy. RICHARD C. BRITTON and PAUL A. NELSON, Cleveland Clinic Foundation, Cleveland.

Use of Exhibits in Teaching. CHARLES D. SHERMAN, JR., University of Rochester School of Medicine and Dentistry, Rochester, New York.

Primary Healing of Skin Wounds Without Sutures. BERNARD J. PISANI, THEODORE GOLDEN, SEYMOUR NASSBERG, and LOUIS M. ROUSSELOT, St. Vincent's Hospital, New York.

Enzyme Debridement in Surgical Lesions. JAMES F. CONNELL, JR., ROBERT WALLACE, and LOUIS M. ROUSSELOT, St. Vincent's Hospital, New York.

Intensive Care Unit. JAMES W. PATE, EDWARD STORER, and HARWELL WILSON, University of Tennessee, Memphis.

Blood Volume Determinations. WARD D. O'SULLIVAN, C. JULES ROMINGER, and RICHARD H. FLANDREAU, Misericordia Hospital, Philadelphia.

Face Masks of Spun Glass Fiber. PAUL S. NICHOLES, University of Utah College of Medicine, Salt Lake City.

Exposed Membrane Oxygenator. PETER C. HOFSTRA, ARMAND A. CRESCENZI, and PHILIP COOPER, Albert Einstein College of Medicine and Bronx Veterans Administration Hospital, New York.

Surgical Special Care Unit. J. MURRAY BEARDSLEY, Rhode Island Hospital, Providence.

Hospital Planning for Disaster. JOHN H. SCHNEEWIND, University of Illinois Research and Educational Hospitals, Chicago.

Therapeutic Engineering in a Modern Hospital. ARTHUR E. MACNEILL, RICHARD W. EGAN, SIDNEY ANTHONE, and ROLAND ANTHONE, University of Buffalo School of Medicine, Buffalo.

UNIVERSITY OF MICHIGAN LIBRARIES

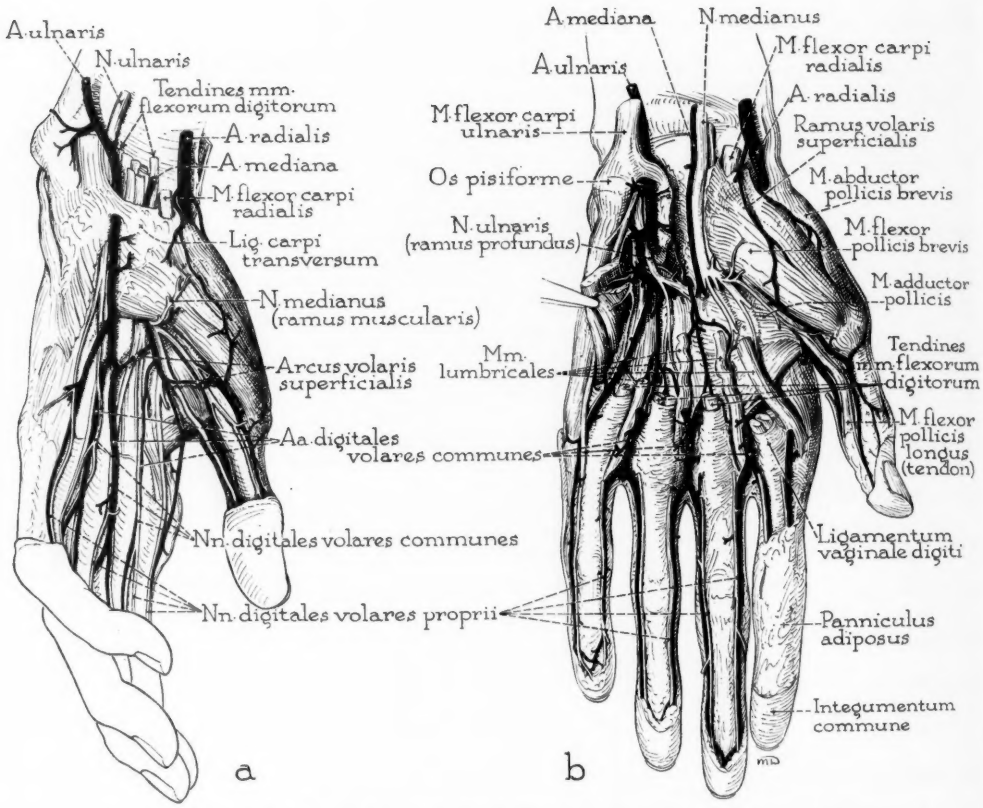


FIG. 1. Arteries of the volar surface of the hand. Dissections of an especially favorable specimen. a, Dissection, viewed from the ulnar (medial) aspect. b, Dissection seen from the palmar aspect. The contributions to the superficial arch have been transected, the long flexor tendon cut.

Arterial Patterns in the Hand Based upon a Study of 650 Specimens.—
Sherman S. Coleman and Barry J. Anson.